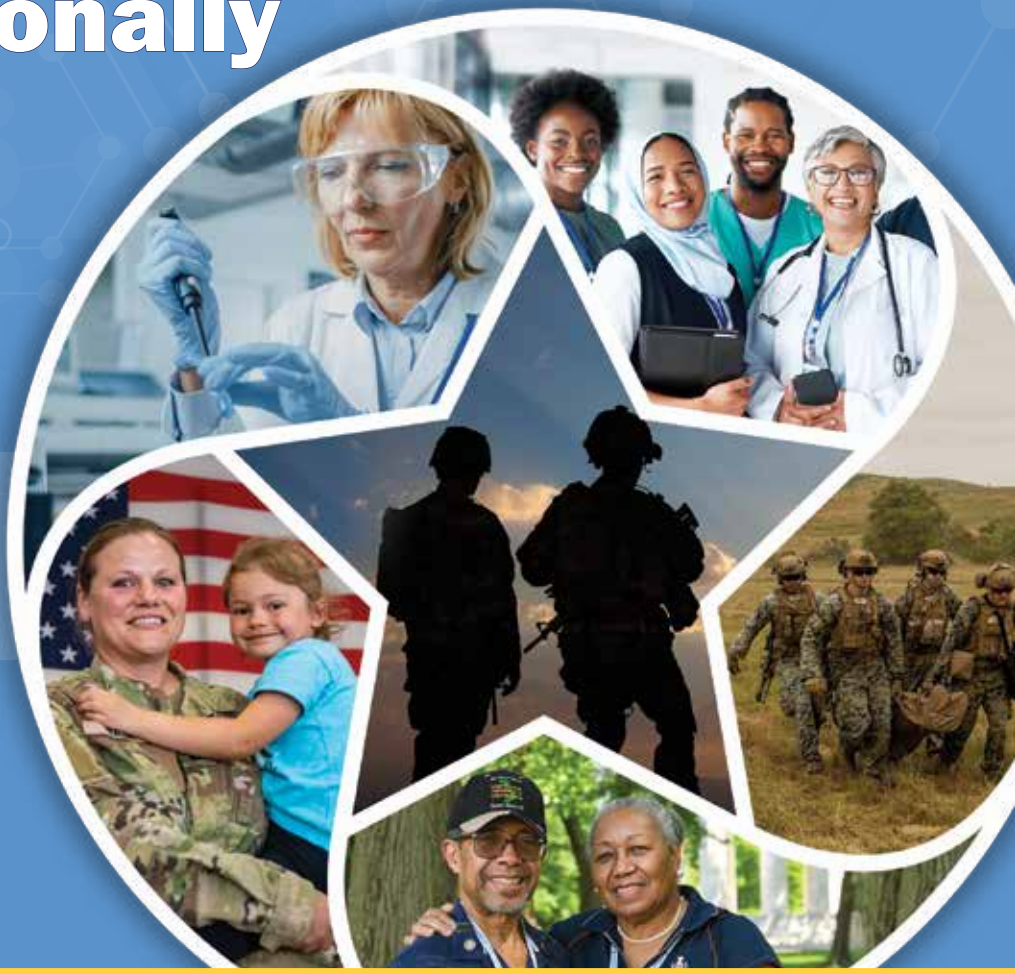
# Congressionally Directed Medical Research Programs

# 2023

## Annual Report



CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

U.S. Army Medical Research and Development Command

*Dear Consumer Advocates, Researchers, Active-Duty and Veteran Members, and Families,*

The Congressionally Directed Medical Research Programs is pleased to present the 2023 Annual Report. Our world is moving faster than ever, and our team of dedicated professionals continually works to stay ahead of the curve, investing in high-impact, innovative research projects that are aimed at treating and curing the diseases and conditions specified by Congress. Our focus will always be centered on the patients, caregivers, and communities that our work directly impacts.

The CDMRP annually adapts each program's vision and investment strategy to allow for rapid response to ever-changing needs. Upon receiving our congressional appropriations, all CDMRP programs re-evaluate their respective strategies and investment plans to ensure we are optimizing the use of our resources. We continue to synchronize with federal and non-federal funders to ensure our strategies are complementary, avoid duplication, and target unfunded and/or unmet gaps in research.

The CDMRP takes great pride in our approach to evaluating medical research and considers this as a primary factor in our ability to support meritorious research to make a difference in the lives of patients and their families. CDMRP's two-tiered application review process is recommended by the National Academy of Science's Institute of Medicine. CDMRP peer and programmatic reviews involve input not only from leading scientists and clinicians but also from patient advocates, who we refer to as consumers. CDMRP consumer reviewers are critical stakeholders who bring a sense of urgency and perspective, and they will always be the "true north" for our programs. The CDMRP realizes the valuable impact of consumer input on many levels, and we are now encouraging their involvement as members of research teams where they are instrumental in the study design and help ensure successful completion of the research.

As a Department of Defense organization, the CDMRP's programs support the health and readiness of our Warfighters and their Families. While some programs address diseases and conditions disproportionately affecting Service Members and Veterans, all programs relate to Family member care, which impacts the ability of our military forces to fulfill their assigned mission. Military readiness depends on the health and well-being of beneficiaries and Families, which ultimately impacts the Military Health System. CDMRP-funded research programs address many diseases and conditions seen frequently in Military Health System medical encounters.

This 2023 Annual Report updates stakeholders on changes to CDMRP-wide policies and practices, describes our investments within the CDMRP's 35 distinct medical research programs, and highlights important research outcomes advancing care and improving lives. With funding opportunities publicly announced and competed, we take pride in our organization's transparency and accountability to stakeholders. We also remain dedicated to maintaining our low management costs, which greatly helps in maximizing the funds available for valuable research.

As always, we are grateful for our partners representing consumer and non-profit organizations; other federal medical research funding organizations, including the National Institutes of Health, the U.S. Department of Veterans Affairs, the Advanced Research Projects Agency for Health, and the Biomedical Advanced Research and Development Authority; and the medical community, academia, industry, the military, and other medical research organizations. Their contributions inform our programs' strategy, and their participation throughout our two-tier review process are integral to our success.

Finally, we are honored that Congress has trusted the CDMRP for more than 30 years to transform health care through innovative and impactful research. We look forward to the many medical breakthroughs that lie ahead.

*Sincerely,*
*Colonel Sarah B. Goldman, Ph.D.*
*Director, CDMRP*
*U.S. Army Medical Research and Development Command*


Department of Defense

U.S. Army Medical Research and Development Command

Congressionally Directed Medical Research Programs

Annual Report

September 30, 2023

Congressionally Directed Medical Research Programs
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# TABLE OF CONTENTS

"Although serving as a consumer reviewer for the Breast Cancer Research Program is a lot of work, it sheds light on the research being done for the various types of breast cancer. I am impressed the BCRP does not focus on just one type of breast cancer, which is of great importance to patients. It is apparent the BCRP panel members are dedicated to the research to understand the causes and progression of breast cancer, ways to improve patient care, and saving lives of breast cancer patients."

*Carmen Pace, Breast Cancer Research Program Consumer Peer Reviewer*

# INTRODUCTION

**CDMRP VISION:** *Transform health care through innovative and impactful research*

**CDMRP MISSION:** *Responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, Veterans, and the American public*

**ABOUT THIS REPORT:** This Annual Report presents CDMRP accomplishments and activities for fiscal year 2023 from October 2022 through September 2023. During this time, the CDMRP completed execution of the FY22 budgetary appropriation totaling $1.54 billion, obligating 100% of the total appropriation received, and initiated execution of the FY23 appropriation of $1.52 billion by hosting stakeholder and vision setting meetings and releasing program announcements to solicit applications to funding opportunities.

CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

# ABOUT THE CDMRP

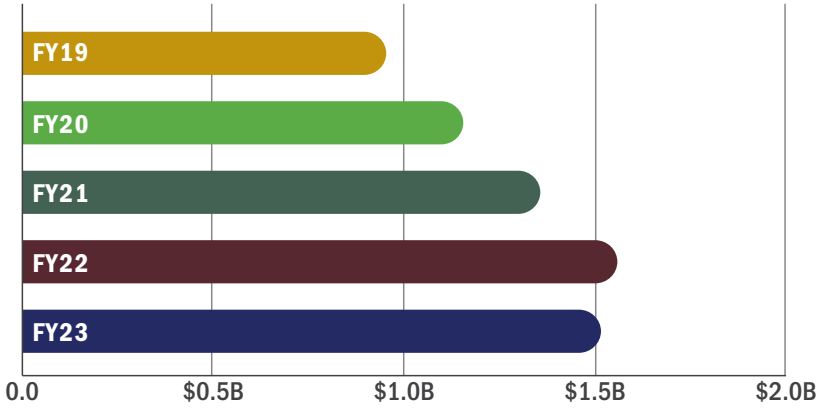
In FY23, Congress appropriated funds for 35 distinct CDMRP programs. Collectively, these programs strive to advance paradigm-shifting research leading to improvements in patient care or breakthrough technologies and resources for clinical benefit. The CDMRP also provides program and award management support as requested to other core Department of Defense medical research programs.

The DOD does not request funding for CDMRP as part of the president's annual budget submission. Instead, in response to input from consumer advocates, survivors, people living with a disease or injury experience, and others, Congress adds funding for the CDMRP into the annual defense appropriations bill.

The CDMRP uses a two-tier review process to develop funding recommendations that balance the most meritorious science across many disciplines and offer the highest promise to fulfill programmatic goals. See Appendix B for an explanation of how the two-tier process works.

**Find out more about the CDMRP by visiting cdmrp.health.mil/aboutus**

## ANNUAL CONGRESSIONAL APPROPRIATIONS




## ACCOMPLISHMENTS AND OUTPUTS AT A GLANCE

Between October 2022 and September 2023, the CDMRP fully executed FY22 appropriations, announced funding opportunities for FY23 programs, and actively managed a portfolio of innovative and impactful research projects relevant to stakeholder needs. This year's efforts include:

**FY22 Appropriations**

**$1.54** billion in appropriations

**35** programs

**1,094** research awards

**$1.39** billion funded research

**FY23 Appropriations**

**$1.52** billion in appropriations

**35** programs

**October 2022–September 2023**

**5,947** managed research awards

**FY23 Research Outputs**

**725** publications

**1,240** presentations

**52** patents

> The CDMRP does a very good job focusing on the fact that military medicine is a continuum of care and doesn't focus on one specific aspect of care. [It] is a critical, non-dilutive funding stream to innovative medical research that ensures the national health enterprise has the most relevant and up-to-date evidence-based medical practices."
>
> *U.S. Army Master Sgt. Sam Patrick,*
> *Combat Readiness – Medical Research Program Peer Reviewer*

# TRANSLATING RESEARCH FROM **BENCH TO BEDSIDE**

The CDMRP invests in groundbreaking research across the full spectrum of medical research and development, including basic, applied, translational, and clinical research. By strategically funding high-risk/high-reward projects and targeting research with the highest potential impact, the CDMRP is able to fill critical gaps related to mechanisms of disease, therapeutic interventions, and development of new technologies. CDMRP-funded research benefits not only military members, military retirees, and Family members, but the civilian population as well.

The percentage of the CDMRP's FY22 investments based on awardee-identified research stage from bench to beside is shown below. See Appendix C for additional information regarding the stages of funded research.

| 29% | 17% | 35% | 19% |
|---|---|---|---|
| **Basic/Discovery Research**<br>*Generating new ideas, knowledge, hypotheses, models* | **Applied Research/ Technology Development**<br>*Building on basic research discoveries* | **Translational Research**<br>*Evaluating the transfer of research results from the laboratory to the clinic prior to executing clinical trials* | **Clinical Research**<br>*Conducting patient-oriented and/or population-based studies with human subjects, including clinical trials* |

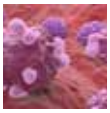
# FY23 IMPACT HIGHLIGHTS

Consistent with the CDMRP's mission to develop and deliver health care solutions, research funded by the CDMRP contributes to development and testing of FDA-regulated drugs and devices, as well as significant changes to clinical practice. The following are select examples of CDMRP-supported development of therapies and diagnostic tools, including products achieving critical FDA regulatory milestones or leading to important changes in clinical practice in 2022 or 2023.

## Clinical Trials

**Prosetin** is an oral therapy designed to enter the brain and **reverse cellular stress** observed in **amyotrophic lateral sclerosis**. Orphan drug designation by the FDA and a phase 1 clinical trial launched in 2022 are taking prosetin to the next level clinically.

An **implantable device** pairing functional electrical nerve stimulation with a brain computer interface **restored upper-limb function and sense of touch** in a clinical trial of people with **spinal cord injuries**.



A **positron emission tomography (PET NaF-18)-based imaging method** is being tested in an early-phase clinical trial, allowing for quicker and easier detection of **ovarian cancer** by identifying metabolic changes at the cellular level.

## Devices

**Wearable microelectromechanical device** provides adaptive and **controlled release of a repellent** for personal protection against ticks, mitigating the incidence of **tick-borne diseases**.

Development of a new **virtual reality cognitive testing platform** offers an improved way to test memory and cognitive abilities for diagnosis of **Alzheimer's disease** using apartment and grocery store settings, which are more familiar to people than a clinician's office.

Development of a **portable system** to **prolong preservation time** of face grafts between procurement and **reconstructive transplantation** that could reduce intragraft inflammation and optimize graft viability.

## Translated to Clinical Use

Kerecis® developed and patented a **fish skin grafting technology** for the **treatment of burns** and other acute and chronic wounds, providing **superior temporary coverage and augmented healing** over cadaver skin grafts.

The HYFTOR™ **sirolimus topical gel** received FDA approval **to treat facial tumors** associated with **tuberous sclerosis complex**, promising to greatly enhance the quality of life for people living with this disease.

**Pylarify®**, an injection-delivered diagnostic imaging agent, received FDA approval for detection of **prostate cancer** tumors via computerized tomography scans.

The **Biotheranostics Breast Cancer Index** test became available to Service Members and their Families through TRICARE. The prognostic test evaluates a patient's initial tumor sample to assist patients and doctors in making **critical decisions regarding treatment plans** for early-stage hormone receptor-positive breast cancer.

A **serum biomarker test** for **multiple sclerosis** received FDA Breakthrough Device Designation as a blood biomarker for the disease, providing a practical alternative to neuroimaging to monitor relapse and treatment outcomes.

Agamree® (vamorolone), a **non-hormonal steroid drug**, received FDA approval for the treatment of **Duchenne muscular dystrophy**. Agamree decreases muscle inflammation with reduced side effects compared to other corticosteroid-based treatments.

"From the moment I was diagnosed with prostate cancer, I began asking the question, 'Why me? Why should I get cancer?' My service as an advocate in the Prostate Cancer Research Program showed me that I was not unique and that the impact of prostate cancer was global, pervasive, and disproportionately biased. These realizations only inspired me to become more involved in the research area, and motivated to support funding for that research that would result potentially in a road towards a cure or, at the least, better management of the disease and a better quality of life for patients."

*Virgil Simons, Prostate Cancer Research Program Programmatic Reviewer*

# CDMRP-FUNDED NOBEL PRIZE LAUREATES

*Over the years, the CDMRP funded groundbreaking researchers who made significant contributions that "conferred the greatest benefit to humankind."*

2022 CAROLYN BERTOZZI, PH.D.

In October 2022, Carolyn Bertozzi, Ph.D., a multiple awardee of the CDMRP, received a 2022 Nobel Prize in chemistry for her work in click chemistry, the process of quickly joining together molecular building blocks to form complex molecules. Bertozzi's CDMRP-funded research laid the foundation for development of targeted imaging agents for non-invasive breast cancer detection and diagnosis, and contributed to the identification of biomarkers to aid in stage-specific prostate cancer detection and to inform treatment decisions.

*Since 2008, an additional four former CDMRP award recipients received recognition for their achievements in chemistry, and physiology or medicine.*

2019 GREGG SEMENZA, M.D.

2019 WILLIAM KAELIN, JR., M.D.

In 2019, Dr. Gregg Semenza and Dr. William Kaelin, Jr., received the Nobel Prize in physiology or medicine for their discoveries of how cells respond to hypoxia, or decreased levels of oxygen. Semenza's CDMRP-funded research focused on inhibiting hypoxia and metabolic enzymes to make breast cancer cells more sensitive to chemotherapy. Kaelin received two CDMRP awards, the results of which shed light on regulation of hypoxia in tuberous sclerosis complex and the identification of biological molecules useful for destabilizing the estrogen receptor, an important advancement in the field of breast cancer.

2009 ELIZABETH BLACKBURN, PH.D.

2008 ROGER TSIEN, PH.D.

Elizabeth Blackburn, Ph.D., a groundbreaking researcher in telomeres, received the 2009 Nobel Prize in physiology or medicine, and Roger Tsien, Ph.D., a pioneer in green fluorescent protein, won the 2008 Nobel Prize in chemistry. Blackburn and Tsein received support from the CDMRP, making new discoveries in breast cancer research.

*The CDMRP is honored to acknowledge the contributions of these award-winning scientists that CDMRP has supported over the past three decades. The achievements of this outstanding group of dedicated researchers will impact our military and civilian populations in a lasting and far-reaching way.*

# INTERAGENCY COLLABORATIONS

Representatives from the NIH, the VA, and other federal funding organizations actively participate on CDMRP peer and programmatic review panels. Over 170 individuals representing other federal organizations served on the FY23 Programmatic Panels. These panel members bring their expert knowledge of the field and their organization's funding strategy to help recommend the best CDMRP investments.

**Individuals from a wide range of government agencies participate in CDMRP programmatic panels.**

**Other Government Agencies**

- *HHS Headquarters*
- *FDA*
- *NIH*
- *National Cancer Institute*
- *National Institute of Neurological Disorders and Stroke*
- *CDC*
- *VA*

**DOD Organizations**

- *DHA*
- *Sensory Systems*
- *TBI*
- *Psychological Health*
- *Musculoskeletal Injury*
- *Defense Advanced Research Projects Agency*
- *Uniformed Services University of the Health Sciences*

The CDMRP communicates and actively coordinates with other biomedical research funding organizations, including federal partners such as the NIH and the VA, as well as non-federal funders, to identify gaps, synergize investments, and prevent duplication of effort. The CDMRP participated in several notable collaboration opportunities this year, including the DHA-sponsored Review and Analysis meetings in which the NIH, the VA, and other federal partners reviewed the current CDMRP research portfolios, the research funding landscape, and strategic priorities. Additional examples of interagency collaborations include, but are not limited to, the following:

The **Innovation Equity Forum** is a global effort co-led by the NIH Office of Research on Women's Health and the Bill and Melinda Gates Foundation, with over 250 steering committee members from over 50 countries and diverse sectors working in women's health. The forum generated a Women's Health Innovation Opportunity Map as a collaborative framework consisting of 50 opportunities with solution strategies to advance women's health innovation. The opportunity map launched in October 2023, and forum efforts will continue, with the goal of realizing the opportunities and strengthening research and development in women's health.

The CDMRP is actively engaged with the **Advanced Research Projects Agency for Health** to foster coordination at both the program and leadership levels, with the goal to maximize the value of funded research while preventing duplication of efforts.

By invitation, the CDMRP participated in **Cancer Moonshot** initiatives, including briefing on global cancer research efforts and data calls for events led by the president and first lady of the U.S.

The VA-led **Research Advisory Committee on Gulf War Veterans' Illnesses** aims to improve the health of ill Gulf War Veterans. The Toxic Exposures Research Program attends regular meetings with the committee to facilitate VA awareness of the program's mission and to help the program focus their priorities, avoid duplication of effort, and maintain focus on stakeholder needs. This coordinated effort also informs ways CDMRP applicants can collaborate with the VA to leverage VA resources.

The CDMRP entered into a Memorandum of Understanding with the HHS's **Biomedical Advanced Research and Development Authority** to strengthen and expand information sharing across areas of common interest such as the treatment of burn and blast injuries, traumatic brain injuries, and wounds; countering the effects of drug-resistant bacteria and specific toxic exposures; and improving

vaccines and diagnostics. This collaborative partnership will accelerate the development of technologies and therapies essential to the Warfighter and the American public.

The **Federal Interagency Workgroup on Autism** is an all-federal group that discusses federal agency and department activities related to autism spectrum disorder. Federal members, which include the DOD, the NIH, the Department of Education, Department of Labor, Social Security Administration, Centers for Disease Control and Prevention, and the Department of Justice, among others, are given the opportunity to discuss plans and emerging initiatives within their organization during several meetings throughout the year. As a member of the workgroup, the additional level of coordination among members allows the Autism Research Program to focus its funding efforts on unmet and underfunded needs of the autism community.

Since the inception of the Peer Reviewed Alzheimer's Research Program, the CDMRP participates on the **National Alzheimer's Project Act**, which includes the HHS, the VA, and the National Science Foundation. The interagency group is working to coordinate research and services across agencies, accelerate the development of Alzheimer's disease/Alzheimer's disease-related dementias treatments, improve early diagnosis and coordination of care, reduce ethnic and racial disparities in rates of disease, and coordinate with international efforts to fight these conditions. In addition, the Peer Reviewed Alzheimer's Research Program provides data and recommendations informing annual updates to the National Plan to Address Alzheimer's Disease.

The **Lupus Federal Working Group** brings together stakeholders with an interest in lupus to share information and coordinate the activities of federal agencies involved in lupus care and research. The working group is led by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and includes representatives from all relevant HHS agencies and other federal departments with an interest in lupus. As a member since FY17, the Lupus Research Program's participation with the working group provides an outlet to share the program's approach and mission with the lupus community.

"It is great to see the passion that the scientific community has for TSC, and I am always amazed at the research proposals that I review. The scientists are so intelligent, and they truly understand the hardships of TSC, both of which drive the science. The researchers are excellent about explaining the science and specific details. In turn, they value our opinions as TSC-affected families."

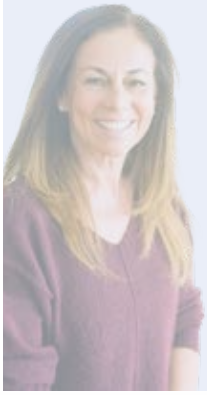
*Heather Harden, Tuberous Sclerosis Complex Research Program Peer Reviewer*

# ENGAGING CONSUMERS

As they have for the past three decades, consumers remain a cornerstone of CDMRP and actively participate throughout our program cycle. They serve alongside scientists, clinicians, and leading experts, holding an equal voice and vote in deliberations and in helping make funding recommendations. Consumers may be a patient, survivor, family member, caregiver, those in partnership with a community-based organization(s), and/or those involved with community advisory boards - all associated with a particular illness or disease. Involvement of consumers integrates the perspectives and needs of the patient community into the research design, execution, and/or dissemination of results, increasing the potential impact of the research results on the target population.

The CDMRP continues to expand the scope of consumer involvement within its research programs. Many programs prioritize including consumers as research team members on funded awards.

**FY23 Consumer Involvement by the Numbers**



**70** consumers served on programmatic panels

**807** consumers served on peer review panels

**40** award mechanisms, released by 19 programs, require or recommend consumer involvement

Across CDMRP award mechanisms, consumers may serve multiple roles within a research team to actively maximize the impact of research. In many cases, consumers are involved in the development of the research question, project design, oversight, recruitment, and evaluation, as well as other significant aspects of the research project. Further, scientific researchers and community members often are required to collaborate and contribute their expertise equitably on all aspects of the particular project.

"My experience with the PRCRP has been positive. Consumer advocates are a bridge between the patient and research community. They are builders of trust and awareness and are essential in protecting and promoting the consumer's welfare and voice. It is our duty and privilege as consumer reviewers to take the needs of our community and be their voice in areas such as the PRCRP. Consumer advocacy is essentially what ensures that needs are being met, and consumers are the builders of awareness and trust."

*Melinda Bachini, Peer Reviewed Cancer Research Program Consumer Peer Reviewer*

# OUR PROGRAMS

The 35 research programs highlighted in this section share many common features, yet each program is unique and emphasizes the specific needs of the research and advocacy communities. These programs are detailed on the following pages.

# ALCOHOL AND SUBSTANCE USE DISORDERS RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Since FY10, the Alcohol and Substance Use Disorders Research Program (ASUDRP) prioritizes congressionally directed medical research on substance use disorders aimed at reducing the overall number of opioid-related overdose deaths.

| *FY22 Congressional Appropriations* |
|---|
| **$4M** |
| *FY22 Research Investment* |
| Modification to ongoing awards . $3,525,000 |
| **Total:** $3,525,000 |
| *FY22 Withholds and Management Costs* |
| USAMRDC .....$77,340 |
| SBIR/STTR ..... $133,000 |
| Mgt Costs (6.98%)..... $264,660 |
| **Total:** $475,000 |

[1] Provisional Drug Overdose Death Counts. 2023. Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. https:// www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data. htm. | [2] Blakey SM, Griffin SC, et. al. 2022. Comparing Psychosocial Functioning, Suicide Risk, and Nonsuicidal Self-Injury between Veterans with Probable Posttraumatic Stress Disorder and Alcohol Use Disorder. *Journal of Affective Disorders* 308:10–18. doi: 10.1016/j.jad.2022.04.006. | [3] Haile CN, Baker MD, et. al. 2022. An Immunoconjugate Vaccine Alters Distribution and Reduces the Antinociceptive, Behavioral and Physiological Effects of Fentanyl in Male and Female Rats. *Pharmaceutics* 14(11), 2290. https:// doi.org/10.3390/ pharmaceutics14112290. | [4] Cruz B, Vozella V, et. al. 2022. FKBP5 Inhibitors Modulate Alcohol Drinking and Trauma-Related Behaviors in a Model of Comorbid Post-Traumatic Stress and Alcohol Use Disorder. *Neuropsychopharmacology* 48, 1144-1154. https://doi.org/10.1038/s41386-022-01497-w.

## WHY IS THERE A NEED FOR ALCOHOL AND SUBSTANCE USE DISORDERS RESEARCH?

**In 2022 in the U.S. population, the provisional drug overdose death count was 110,000 and over 80,000 deaths were related to opioid use[1]**

**Veterans with PTSD and alcohol use disorder: [2]**

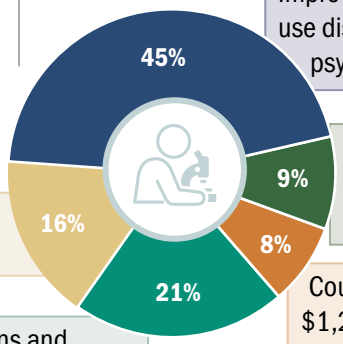
- **Are at much higher risk for suicide**
- **Exhibit more severe and treatment-resistant symptoms than Veterans who have either disorder alone**

## HOW IS THE PROGRAM ADVANCING ALCOHOL AND SUBSTANCE USE DISORDERS RESEARCH?

The ASUDRP established three priority aims (top) and directed FY22 investments into five focus areas (bottom).

**For those with ASUD and co-occuring PTSD, and other psychological disorders**

| | |
|---|---|
| **Aim 1: Discover** | Testing new chemical entities and repurposing existing medications in preclinical and nonclinical models |
| **Aim 2: Proof of Concept** | Human studies of potential medications, including assessment of medical safety and doses for potential efficacy studies |
| **Aim 3: Phase 2 Efficacy** | Multi-site clinical trials to test potential medications in humans, as well as explore precision medicine tools for matching patients to these medications |




Improve treatment for alcohol and substance use disorders with co-occuring PTSD and other psychological disorders, $7,401,904

Improve treatment compliance, prevent relapse, and reduce risk of misuse through medications, $1,507,141

Counteract opioid overdose, $1,224,797

Test novel medications and immunotherapies, $3,469,537

Identify new medication targets, $2,661,538

**PROGRAM MISSION:** *To explore integrated approaches to address alcohol and substance use disorders, and reduce the number of opioid and other substance use-related deaths, through multidisciplinary, team-based research efforts that translate basic knowledge into enhanced clinical pharmacological treatment protocols and enhanced quality of life for Service Members, Veterans, and the American public*

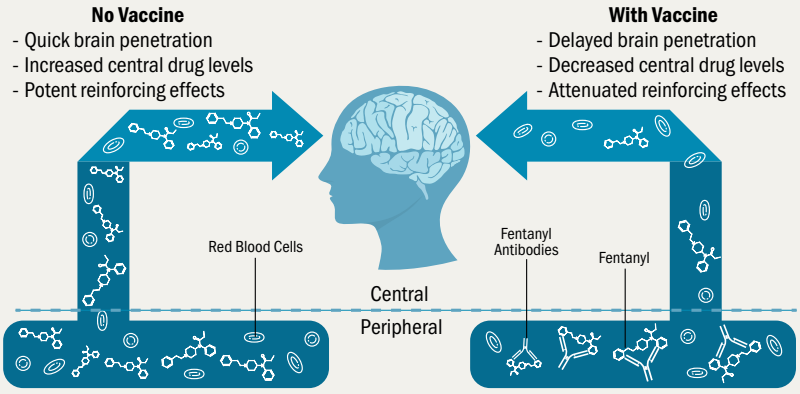
## HOW IS THE PROGRAM MAKING AN IMPACT?

**Drug Overdose Vaccine**

### *Using an Anti-Fentanyl Vaccine to Treat Opioid Use Disorder and Overdose*

*Colin Haile, M.D., Ph.D., University of Houston*

Two studies conducted by the research team resulted in the development of a vaccine to block fentanyl from entering the brain and preventing the harmful effects of the drug. This new vaccine could potentially work as a **relapse prevention agent** and protect against accidental exposures. Recent findings from these studies were published in the journal, *Pharmaceutics*.[3]




**Drug Library**

### *Creating a Library of Drug Compounds for Use in Treating Alcohol and Substance Use Disorders*

*Todd Webb, Ph.D., RTI International*

*LiRong Wang, Ph.D., University of Pittsburgh*

Investigators funded by the program are developing an interactive library of compounds available for repurposing as a treatment for alcohol and substance use disorders co-occurring with PTSD and/or other psychological disorders. This library will **harmonize and integrate the research findings** from the existing funded non-clinical studies supported by the research program. By gaining greater access to information on existing compounds through an easy to use web-based platform with supporting evidence, potential applicants will be able to enhance their proposed research proposals.

**Potential New Pharmacotherapy**

### *Preclinical Testing of a Drug Compound for Treating Alcohol Use Disorders that are Co-occurring with PTSD*

*Marisa Roberto, Ph.D., The Scripps Research Institute*

The gene FKBP5 is linked to stress-related disorders. Investigators tested two compounds, benztropine and SAFit2, which inhibit FKBP5. They found the compounds successfully modulated trauma-related alcohol drinking and some PTSD-like behavioral symptoms in laboratory rats. The two compounds also appear to be more effective at modulating alcohol drinking in male rats than in female rats. These outcomes suggest targeting the protein FKBP5, and other similar proteins may help improve alcohol use disorders co-occurring with PTSD. These agents may be particularly **relevant for clinical translation to pharmacotherapies for Service Members and Veterans.**[4]

"As a behavioral healthcare provider, I routinely witness the negative impact of substance abuse on active-duty Service Members and Veterans alike. It has been a privilege to be a part of the team that supports the effort to combat these disorders."

***U.S. Army Maj. Yosef Fufa, D.N.P., P.M.H.N.P-B.C., Carl R. Darnall Army Medical Center, Programmatic Panel Member, FY22-FY23***

# AMYOTROPHIC LATERAL SCLEROSIS RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

The Amyotrophic Lateral Sclerosis Research Program (ALSRP) was established in 2007 to advance treatments for people living with amyotrophic lateral sclerosis.

| *FY22 Congressional Appropriations* |
|---|
| **$40M** |
| *FY22 Research Investment* |
| Clinical Biomarker Development Award ..... $6,468,772 |
| Pilot Clinical Trial Award ..... $5,052,493 |
| Therapeutic Development Award ..... $7,069,662 |
| Therapeutic Idea Award ..... $17,505,838 |
| Modification to ongoing awards ..... $2,905 |
| **Total:** $36,099,671 |
| *FY22 Withholds and Management Costs* |
| USAMRDC ..... $773,300 |
| SBIR/STTR ..... $1,335,000 |
| Mgt Costs (4.73%) ..... $1,792,029 |
| **Total:** $3,900,329 |

"The advancements made because of this funding have been instrumental to changing treatment paradigms, discovering new potential drug targets, and advancing early phase clinical trials. Since the inception of this program in 2007, progress towards meaningful treatment has been accelerated beyond a pace my family ever dreamed of back when my father lost his battle to the disease in 2003."

***U.S. Air Force Maj. Timothy Fullam, M.D., Medical Corps, Programmatic Panel Member, FY22-23***

## WHY IS THERE A NEED FOR ALS RESEARCH?

**Research shows Veterans are 50% more likely to develop ALS**[1]

**1 in 6** people living with ALS are Veterans[1]

**ALS is always fatal**[2]

- Most patients succumb to the disease within **2-5 years** of diagnosis[3]
- On average, **5,000** new patients are diagnosed every year[4]
- By 2040, incidence is predicted to increase worldwide by **70%**[5]
- 90% of ALS cases have no known hereditary cause[4]

## HOW IS THE PROGRAM ADVANCING ALS RESEARCH?

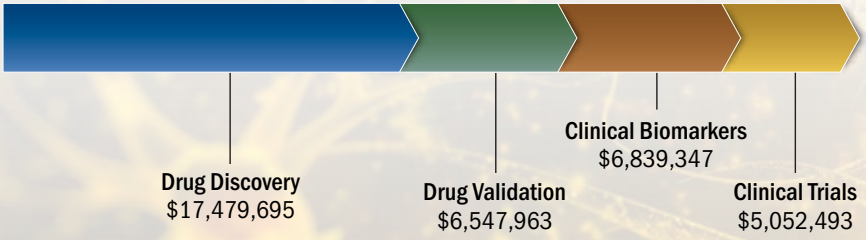
In FY22, the ALSRP addressed four strategic program priorities (top) and invested across the treatment delivery pipeline (bottom).

Support highly innovative ideas for new therapeutics

Fund a drug development pipeline

Support biomarker utilization to better define ALS subtypes, predict therapeutic response, and improve prognosis

Fund early phase trials to inform, de-risk, and accelerate large later-stage trials




[1] Weisskopf M, O'Reilly M, et al. 2005. Prospective Study of Military Service and Mortality from ALS. *Neurology* 64(1). | [2] The Johns Hopkins University: Amyotrophic Lateral Sclerosis (ALS). 2023. https://www.hopkinsmedicine.org/health/conditions-and-diseases/amyotrophic-lateral-sclerosis-als. | [3] Larson TC, Kaye W, et al. 2018. Amyotrophic Lateral Sclerosis Mortality in the United States, 2011-2014. *Neuroepidemiology* 51(1-2):96-103. | [4] Mehta P, Raymond J, et al. 2023. Prevalence of Amyotrophic Lateral Sclerosis in the United States Using Established and Novel Methodologies, 2017. *Amyotrophic Lateral Sclerosis Frontotemporal Degeneration* 24(1-2):108-116. | [5] Arthur KC, Calvo A, et al. 2016. Projected Increase in Amyotrophic Lateral Sclerosis from 2015 to 2040. *Nature Communications* 7:12408. | [6] Baloh RH, Johnson JP, et al. 2022. Transplantation of Human Neural Progenitor Cells Secreting GDNF into the Spinal Cord of Patients with ALS: A Phase 1/2a Trial. *Nature Medicine* 28:1813–1822. https://doi.org/10.1038/s41591-022-01956-3.

**PROGRAM MISSION:** *Fund impactful research to develop ALS treatments*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Drug Screening Platform**

***New Nerve-on-a-Chip® System Could Revolutionize Therapeutic Development***

*Jabe Curley, Ph.D., AxoSim Technologies*

The team performed the first known functional in vitro measurement of ALS biomarkers on a 3D platform, called a Nerve-on-a-Chip®. This project sought to create a **commercial-ready, clinically relevant, preclinical model** for developing therapeutics addressing the inadequacy of current preclinical drug screening tools used to diagnose this complex neurodegenerative disease. The research team anticipates the Nerve-on-a-Chip® will serve as a platform **accelerating drug discovery** towards clinical trials.

**Cell-Based Therapy**

***A Combined Cell and Gene Therapy Approach for Preserving Motor Neuron Function***

*Clive Svendsen, Ph.D., Cedars-Sinai Medical Center*

In an effort to prevent the degradation of motor neuron function, Svendsen's team delivered cells engineered to secrete **GDNF, a growth factor that promotes the survival of motor neurons**, into the outermost neural tissue surrounding the brains of symptomatic animals. The growth factor improved their motor neuron function, which **delayed disease progression** and enabled the animals to live longer. As reported in a 2022 Nature Medicine article, the team reported successful clinical trial results indicating patients who received the therapy showed no negative effects on leg muscle strength. This is the first in-human study to show that neural cells engineered to release GDNF can be safely transplanted into the human central nervous system.

**Disease Progression Biomarkers**

***A Search for Biomarkers to Track Disease Progression***

*Ernest Fraenkel, Ph.D., Massachusetts Institute of Technology*

Fraenkel's team analyzed plasma samples to **identify biological changes** over time in people with ALS. They found that there were several different subtypes of the disease, each with its own molecular signals of progression. The biomarkers identified through this research could impact the **design of clinical trials and the validation of potential therapeutics** to slow or halt disease progression.

**Voice Synthesis**

***A Promising Therapy to Restore Naturalistic Speech in Individuals Affected by the Disease***

*Sergey Stavisky, Ph.D., University of California, Davis*

This project focused on developing a brain-computer interface to provide **instantaneous voice synthesis** for people with amyotrophic lateral sclerosis. The device will utilize an emerging type of medical technology bypassing the damaged parts of the nervous system and connects healthy parts of the brain to a computer. Through this research, the team plans to develop **a neuro-prosthetic device** for people living with the disease to fluently perform activities such as talking or singing.

# AUTISM RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY07, the Autism Research Program (ARP) supports research that seeks to understand the environmental causes of autism spectrum disorders in order to stem the increasing prevalence of autism that could impact the pool of potential candidates for military service.

| *FY22 Congressional Appropriations* |
|---|
| **$15M** |
| *FY22 Research Investment* |
| Career Development Award.....$2,610,494 |
| Clinical Trial Award.....$6,113,158 |
| Idea Development Award.....$4,839,092 |
| **Total:** $13,562,744 |
| *FY22 Withholds and Management Costs* |
| USAMRDC.....$289,944 |
| SBIR/STTR.....$501,000 |
| Mgt Costs (4.55%).....$646,312 |
| **Total:** $1,437,256 |

[1] Military Health System (MHS) data from the Defense Medical Surveillance System, 2010-2019. The Armed Forces Health Surveillance Division, Defense Health Agency, Silver Spring, Maryland, November 2020. | [2] Maenner MJ, Warren Z, et al. 2023. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 years – Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2020. *Morbidity and Mortality Weekly Report. Surveillance Summaries* 72(No. SS-2):1- 14. | [3] Dietz PM, Rose CE, et al. 2020. National and State Estimates of Adults with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders* 50(12):4258-4266. https://www.ncbi.nlm.nih. gov/pmc/articles/PMC9074281/. | [4] Leigh JP, Du J. 2015. Brief Report: Forecasting the Economic Burden of Autism in 2015 and 2025 in the United States. *Journal of Autism and Developmental Disorders* 45(12):4135-9. doi: 10.1007/s10803-015-2521-7.

## WHY IS THERE A NEED FOR AUTISM RESEARCH?

**Over a 10-year period, there were**

**62,550**

**newly diagnosed cases of autism spectrum disorder within the MHS**

***71%*** *of these cases affected beneficiaries of active duty and the Reserve Component*[1]

**Among children 8 years of age in the U.S., an estimated 1 in 36 may have the disorder**[2]

**Currently, it is estimated over 5 million adults in the U.S. have autism**[3]

The cost of caring for those with autism in the U.S. is projected to rise to **$461 billion** by 2025[4]

## HOW IS THE PROGRAM ADVANCING AUTISM RESEARCH?

The ARP leveraged four strategic goals (top) aligned to 17 program priorities (bottom), five of which were funded in FY22 (bold).


### PROGRAM PRIORITIES FUNDED IN FY22

**Assess novel therapeutics ($2,241,493)**

**Develop training or tools to improve healthcare delivery ($749,143)**

**Improve diagnosis and access to services ($4,968,665)**

**Mechanisms underlying conditions co-occurring with ASD ($2,640,148)**

**Pharmacological therapies ($2,963,295)**

### OTHER PROGRAM PRIORITIES

Cultural, socioeconomic, and gender factors in diagnosis, treatment, delivery, and services

Dissemination/ implementation of interventions

Impact quality of life during geographic relocation

Mechanisms underlying sex differences and heterogenous clinical expression of ASD

Factors and Interventions that support adults with ASD and transition to adulthood

Environmental risk factors

Test and rapidly deploy evidence-based practices into the community

Understanding heterogeneity in treatment response

Non-pharmacological therapies

Support pragmatic trials and Long-term treatment outcomes from previous clinical trials

**PROGRAM MISSION:** *Promote innovative research that advances the understanding of autism spectrum disorders and leads to improved outcomes for Service Members, their Families, and the American public*

## HOW IS THE PROGRAM MAKING AN IMPACT?

### *The Influence of Social, Educational, and Work Experiences on Psychological Health for Transition-Aged Youth with Autism Spectrum Disorders*

*Julie Taylor, Ph.D., (top) Vanderbilt University Medical Center*

*Somer Bishop, Ph.D., (bottom) University of California, San Francisco*

Adolescents and adults with autism spectrum disorder experience **higher rates of depression** during their lifetime compared to typically developing individuals and those with other developmental disabilities.[4] Taylor and Bishop are working to identify day-to-day experiences associated with depressive symptoms and quality of life among adolescents and young adults with autism. Using survey data, diagnostic interviews, and end-of-day reports collected from 252 youths and their parents, they are examining how those factors affect their educational, vocational, and social experiences. Preliminary analyses are uncovering important associations that shed light on how day-to-day activities relate to depression and quality of life. The knowledge gained from this project may inform clinical efforts that could **improve psychological health** in adolescents and young adults with autism.

[4] Lever AG, Geurts HM. 2016. Psychiatric Co-Occurring Symptoms and Disorders in Young, Middle-Aged, and Older Adults with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders* 46(6):1916-1930. | [5] Duncan AW, Bishop SL. 2015. Understanding the Gap Between Cognitive Abilities and Daily Living Skills in Adolescents with Autism Spectrum Disorders with Average Intelligence. *Autism* 19(1):64-72.

### *Surviving and Thriving in the Real World: a Daily Living Skills Intervention for High Schoolers with Autism Spectrum Disorder*

*Amie Duncan, Ph.D., Children's Hospital, Cincinnati*

"Surviving and Thriving in the Real World," or STRW, is a group intervention developed to assist autistic adolescents without an intellectual disability to learn age-appropriate daily living skills. Autistic teens often lag 6-8 years behind their chronological age when developing daily living skills that are critical for success in adulthood such as hygiene, cooking, cleaning, navigating the community, and managing money. To test the effectiveness and refinement of the STRW intervention, Duncan conducted a randomized controlled trial of 72 autistic teens in the 11th and 12th grades. Results indicated that those receiving this 14-week intervention **gained 2-3 years of daily living skills** as compared to a social skills control group. **These results are clinically meaningful as they closed the gap between chronological age and daily living skills, which may lead to a more successful adult outcomes**.

### *A Multidisciplinary Intervention for Fecal Incontinence in Children with Autism Spectrum Disorder*

*Nathan Call, Ph.D., BCBA-D, Emory University*

Fecal incontinence impacts quality of life for those affected by autism spectrum disorder, but interventions addressing this concern are lacking. Call conducted a two-week multidisciplinary study to test the efficacy of a **new intervention that incorporates medical and behavioral approaches for addressing incontinence.** Significant improvements in bowel movements were observed in participants receiving the new intervention compared to those receiving the current treatment regimen. Results of this study could inform clinical guidelines for providers treating those with the disorder and, as a result, may **improve quality of life** by reducing the negative effects of toileting accidents, increase community inclusion, remove barriers to social and adaptive skill development, and decrease parental stress.

"The CDMRP's strongest point is the apex where clinicians, researchers and community advocates meet at Programmatic Review. Everyone's input is equally valued and heard. The end result is the funding of game-changing research directly relative to the community seeking more immediate change in improving health outcomes and quality of life. It is an honor to serve on this committee as a community advocate."

***Shelley Hendrix McLaughlin, Unlocking Autism, Programmatic Panel Member, FY07-FY23***

# BONE MARROW FAILURE RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY08, the Bone Marrow Failure Research Program (BMFRP) supports research into acquired and congenital bone marrow failure diseases and syndromes aiming to address fundamental knowledge gaps that may lead to prevention, treatment, and eventual cures.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$7.5M** | |
| *FY22 Research Investment* | |
| Idea Development Award | $5,211,850 |
| Investigator-Initiated Research Award | $1,416,000 |
| **Total:** | $6,627,850 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $145,000 |
| SBIR/STTR | $250,000 |
| Mgt Costs (6.72%) | $477,150 |
| **Total:** | $872,150 |

[1] Military Health System (MHS) data from the Defense Medical Surveillance System. The Armed Forces Health Surveillance Division. Defense Health Agency, 2010-2019. November 2020.

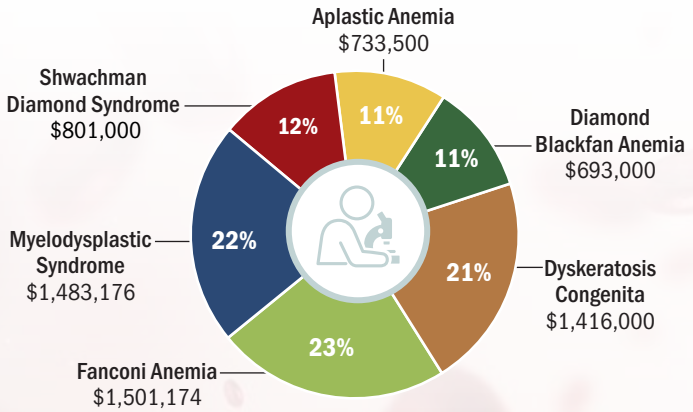
## WHY IS THERE A NEED FOR BONE MARROW FAILURE RESEARCH?

**Over a 9-year period, Service Members with:**

- **acquired** bone marrow failure registered **6,218** outpatient encounters, while DOD beneficiaries registered **718,363**[1]
- **inherited** bone marrow failure registered **12,973** outpatient encounters, while DOD beneficiaries registered **352,677**[1]

## HOW IS THE PROGRAM ADVANCING BONE MARROW FAILURE RESEARCH?

The BMFRP directed FY22 investments into six disease types (top) supporting research that addresses the program's two overarching priorities (bottom).




**Understand the causes and progression of the disease**

**Find effective treatments and cures**

"My reasons for participating in the BMFRP as a Consumer Reviewer are simple: To have some small impact in advancing research that leads to breakthroughs that save lives. Going through a stem cell transplant, despite advances in positive outcomes, is still very risky. The research that gets funded through the program results in treatments, medicines or therapies that hopefully prevents the need for stem cell transplant. The benefit to the patient and family is returning to a quality of life as good or better than before their disease. But my strongest motivation for participating is to pay tribute to those people I have met on this journey that were not as fortunate as me and did not survive their bone marrow failure."

***Rob Minton, Geotab, Peer Reviewer, FY21***

**PROGRAM MISSION:** *To encourage and support innovative research that is committed to advancing the understanding and treatment of inherited and acquired bone marrow failure diseases, thereby improving the health of affected Service Members, Veterans, and the public, with the goal of prevention and cure*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Molecular Biology**

***Potential Treatment for Myelodysplastic Syndromes***

*Annalisa Di Ruscio, Ph.D., Beth Israel Deaconess Medical Center*

Myelodysplastic syndromes can progress to acute myeloid leukemia in nearly 30% of diagnosed cases. These symptoms are caused by a change in DNA, in a process called methylation, which silences genes that normally prevent tumor growth. Di Ruscio's team identified a way to use small fragments of RNA as a tool to block the occurrence of the DNA methylation error, thereby **restoring normal activity of the tumor suppressor genes**.

**Effective Treatments**

***Unraveling the Role of DDX41 in Blood Cell Production and Myelodysplastic Syndromes***

*Teresa Bowman, Ph.D., Albert Einstein College of Medicine*

Myelodysplastic syndromes are a group of rare blood disorders typically manifested in older adults, and the exact incidence is not well-defined. Recent discoveries of an inherited mutation in a gene, called DDX41, opened new avenues of investigation for the research community. Bowman and her team explored these mutations and determined that DDX41 alterations lead to increased DNA damage and genomic instability that ultimately results in anemia. The team discovered blocking activation of the signaling pathway, called ATM, partially suppressed anemia caused by **DDX41 mutations.[2] These findings unveil a critical role that DDX41 could potentially regulate proper red blood cell development, preventing anemia in myelodysplastic syndromes**.

**Improve Treatments**

***Using Nemo-Like Kinase to Treat Diamond-Blackfan Anemia***

*Kathleen M Sakamoto, M.D., Ph.D., Stanford University*

Dr. Sakamoto and team found an enzyme, called Nemo-like kinase, plays a key role in the development of Diamond-Blackfan anemia, an inherited bone marrow failure syndrome characterized by defects in red blood cell development, congenital abnormalities, and vulnerability to cancer. The research team demonstrated the combination of the NLK inhibitor SD208 with the crucial amino acid leucine can increase red blood cell production and regulation of cell-growth. Sakamoto is **currently investigating ways to utilize these findings to improve treatments for patients**.

**Effective Treatments**

***Understanding the Genetic Mutation Behind Poikiloderma with Neutropenia***

*Luis Batista, Ph.D., Washington University in St. Louis*

Poikiloderma with neutropenia is a rare, inherited bone marrow failure disease causing deficient blood development, skin lesions, and a compromised immune system. Patients diagnosed with this disease experience mutations in the gene for the USB1 enzyme, which is important for protection of RNA molecules. If RNA becomes damaged or dysregulated, cells may not correctly function. Batista's team found in cells with USB1 mutations, treatment with a drug, called RG7834, restores levels of specific types of microRNAs that play a role in the production of blood cells. **The advancements discovered through this research can lead to the development of more effective treatments for poikiloderma with neutropenia in other studies**.

[2] Weinreb JT, Gupta V, et al. 2022. Ddx41 Inhibition of DNA damage Signaling Permits Erythroid Progenitor Expansion in Zebrafish. *Haematologica* 107(3):644-654. doi: 10.3324/haematol.2020.257246.

# BREAST CANCER RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in 1992, the Breast Cancer Research Program (BCRP) enables researchers to propose innovative ideas that address the urgent need to end breast cancer. The program challenges scientists to pursue high-risk, high-reward research, explore new paradigms that could lead to critical discoveries, engage in productive collaborations, and make an unprecedented impact on breast cancer.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$150M** Breast Cancer Research Program | |
| **$523,346** From the Stamp Out Breast Cancer Act | |
| *FY22 Research Investment* | |
| Breakthrough Award - Funding Levels 1 & 2 | $53,265,686 |
| Breakthrough Award - Funding Level 3 | $10,494,645 |
| Clinical Research Extension Award | $45,433,844 |
| Era of Hope Scholar Award | $14,984,293 |
| Expansion Award | $3,462,917 |
| Modification to ongoing awards | $6,656,484 |
| **Total:** | $134,297,869 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $2,323,804 |
| SBIR/STTR | $5,003,000 |
| Mgt Costs (6.24%) | $8,898,673 |
| **Total:** | $16,225,477 |

## WHY IS THERE A NEED FOR BREAST CANCER RESEARCH?

**For females 40-59 years of age, the incidence rate of breast cancer is higher in active duty Service Members compared to the general population[1]**

**The incidence rate for active-duty females is**

**7X higher**

**than the average rate of 15 other cancer types across all components of the military[2]**

### 2023 estimations within the U.S.[3]

*Incidence:*

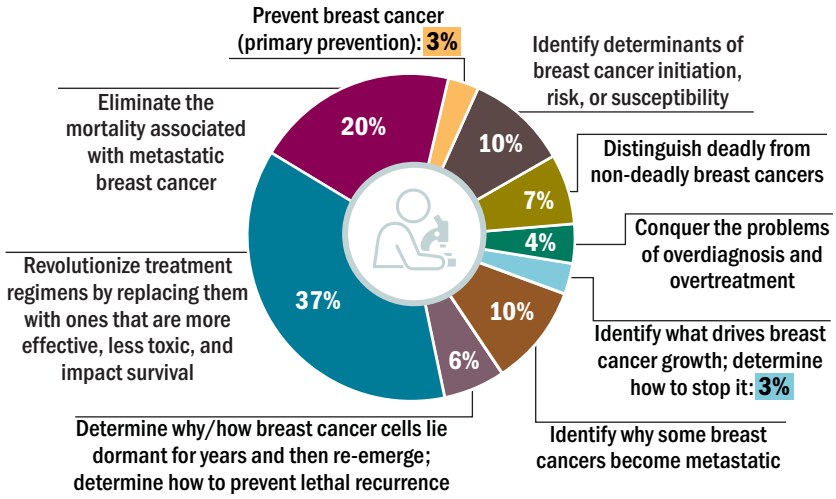
- **297,790** women and **2,800** men will be diagnosed with invasive breast cancer[3]
- **55,720** women diagnosed with ductal carcinoma in situ[3]

*Recurrence and Mortality:*

- An estimated 20%–30% of women diagnosed with invasive breast cancer will have a recurrence in her lifetime[4]
- **43,170** women and **530** men will die[3]

## HOW IS THE PROGRAM ADVANCING BREAST CANCER RESEARCH?

The BCRP directed FY22 investments according to nine program priorities.




[1] Bytnar JA, McGlynn KA, et al. (2023) Cancer incidence in the US military: An updated analysis. *Cancer* 130(1): 96-106. doi:10.1002/cncr.34978. | [2] Lee T, Williams VF, et al. 2016. Incident Diagnoses of Cancers in the Active Component and Cancer-Related Deaths in the Active and Reserve Components, U.S. Armed Forces, 2005-2014. *Medical Surveillance Monthly Report* 23(7):23-31. | [3] Cancer Facts & Figures. 2023, American Cancer Society. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/2023-cancer-facts-figures.html. | [4] Harris, J, Lippman, M, and Osborne, C. 2000. Diseases of the Breast. Second Edition. Philadelphia, PA: Lippincott Williams & Wilkins.

**PROGRAM MISSION:** *To end breast cancer for Service Members, Veterans, and the general public by funding innovative, high-impact research through a partnership of scientists and consumers*

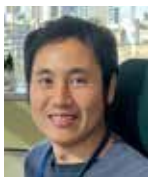
## HOW IS THE PROGRAM MAKING AN IMPACT?

### RESEARCH ADVANCES FOR BREAST CANCER TREATMENT


***Novel Tubulin Inhibitor***

*Wei Li, Ph.D., and Tiffany Seagroves, Ph.D., University of Tennessee Health Science Center*

The research team demonstrated that a novel compound, CH-2-77, which targets proteins called tubulins, overcomes taxane resistance and inhibits tumor growth in models of triple-negative breast cancer, an aggressive subtype of the disease. Their findings support the further development of CH-2-77 and similar drugs to **provide greater treatment options for patients with triple-negative breast cancer**.



***Improved Drug Delivery to Fight Breast Cancer Tumors***

*Kyoji Tsuchikama, Ph.D., UTHealth Houston*

This project examined the effectiveness of a dual drug therapy that uses a linker to combine two cancer-fighting drugs to a tumor targeting antibody. The researchers demonstrated **precise targeting of tumors** and effective drug delivery in breast cancer models. The therapeutic potential of this demonstration represents a promising next step toward **improving breast cancer treatment effectiveness and overcoming drug resistance**.

### BCRP-FUNDED CLINICAL TRIALS OPENED IN 2023


***Integrative Subtype-Targeted Therapeutics – Phase 2***

*Christina Curtis, Ph.D., and Jennifer Caswell-Jin, M.D., Leland Stanford Junior University*

This trial is evaluating the effectiveness of agents targeting specific genetic changes found in hormone receptor positive/HER2-negative breast cancers compared with standard endocrine therapy. Findings from this trial have the potential to inform therapy decision making for high-risk patient subgroups. This therapeutic approach could lead to **reduced breast cancer mortality by preventing relapse and providing new options to treat relapse if it occurs**.


***Functional Precision Oncology – Phase 2***

*Christos Vaklavas, M.D., and Alana Welm, Ph.D., University of Utah*

Towards Personalized Medicine: Patient-Derived Breast Tumor Grafts as Predictors of Relapse and Response to Therapy II, also known as TOWARDS-II, aims to predict, prevent, and treat recurrence in individual patients with low hormone receptor/HER2-negative or triple-negative breast cancer. This study **could establish a new approach for personalized medicine that identifies patients likely to have a recurrence of their cancer**. This approach would also allow for personalized treatments when cancer recurs, sparing patients from toxicities of ineffective drugs and improving survival.

"The DOD BCRP plays a huge role in change for breast cancer by looking at the community as a whole, from early to late-stage breast cancer. When it comes to advancing treatment for breast cancer, all stages are important."

***Leslie Falduto, Metavivor, FY18-FY21 Consumer Peer Reviewer***

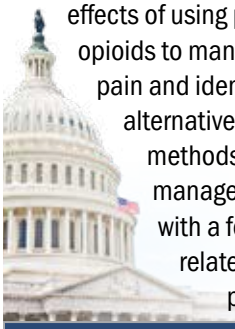
"I am encouraged by the track record of therapies that have been developed with BCRP funding, and my participation in the process of reviewing proposed research makes me hopeful."

***Jamil Rivers, Susan G. Komen, FY19-FY22 Consumer Peer Reviewer***

# CHRONIC PAIN MANAGEMENT RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in 2019, the Chronic Pain Management Research Program (CPMRP) conducts research on the effects of using prescription opioids to manage chronic pain and identifies opioid-alternative or non-addictive methods to treat and manage chronic pain, with a focus on issues related to military populations.



| *FY22 Congressional Appropriations* | |
|---|---|
| **$15M** | |
| *FY22 Research Investment* | |
| Clinical Exploration Award | $2,338,198 |
| Investigator-Initiated Research Award | $10,564,549 |
| Translational Research Award | $0 |
| **Total:** | $12,902,747 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $284,689 |
| SBIR/STTR | $501,000 |
| Mgt Costs (9.23%) | $1,311,564 |
| **Total:** | $2,097,253 |

## WHY IS THERE A NEED FOR CHRONIC PAIN MANAGEMENT RESEARCH?

**Chronic pain affects 31%-44% of Service Members[1]**

**7.1% of active-duty Soldiers experience migraine pain[2]**

**The most prevalent types of chronic pain for active duty Soldiers are[2]:**
**Back and neck pain *(22%)***
**Non-traumatic joint disorders *(28%)***
**Other musculoskeletal pain *(30%)***

- **~20.4%** of American adults experience chronic pain[3]
- **~8.0%** of American adults experience high-impact chronic pain[2]
- In the U.S., chronic pain accounts for **an estimated $560 billion each year** in direct medical costs, lost productivity, and disability programs[2]

## HOW IS THE PROGRAM ADVANCING CHRONIC PAIN MANAGEMENT RESEARCH?

The CPMRP identified six award mechanism-specific program priorities (left) and leveraged FY22 investments into seven pain classification categories (right).

### *Clinical Exploration Award*

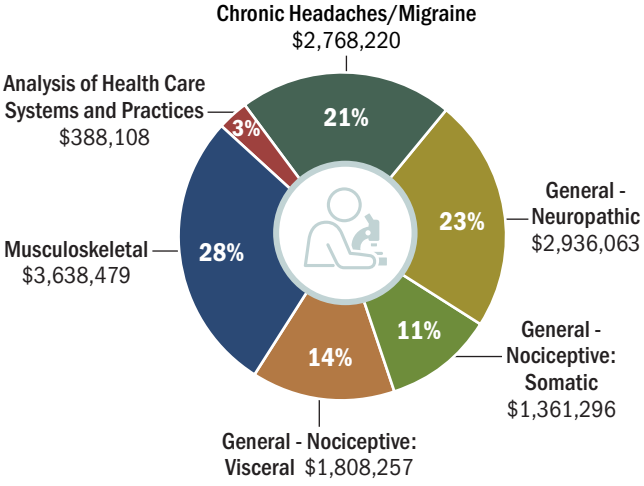
- Chronification of pain
- Effectiveness or observational studies of novel treatments for untested techniques

### *Translational Research Award*

- Implementation science
- Observational studies
- Comparative effectiveness

### *Investigator-Initiated Research Award*

- Chronification of pain
- Effectiveness or observational studies of novel treatments for untested techniques
- Development of non-opioid therapies/methods for treatment




[1] Sherry TB, Roth CP, et al. 2021. Chronic Pain Among Service Members: Using Administrative Data to Strengthen Research and Quality Improvement. Santa Monica, CA: RAND Corporation. https://www.rand.org/pubs/research_reports/RRA1160-1.html. | [2] Reif S, Adams RS, et al. 2018. Prevalence of Pain Diagnoses and Burden of Pain Among Active Duty Soldiers, FY2012. *Military Medicine* 183(9-10):e330-e337. doi: 10.1093/milmed/usx200. | [3] Dahlhamer J, Lucas J, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain among Adults—United States, 2016. *Morbidity and Mortality Weekly Report.* 2018;67(36):1001-1006. https://dx.doi.org/10.15585/mmwr.mm6736a2.

**PROGRAM MISSION:** *To support and promote innovative, high-impact research to prevent the development and improve the management of chronic pain*

## HOW IS THE PROGRAM MAKING AN IMPACT?

***Using Antibodies to Block Receptors for the Treatment of Chronic Pain***

*Karin Westlund, Ph.D., University of New Mexico Health Sciences Center*

Continuing their effort in developing non-opioid therapies that prevent and treat chronic pain, Westlund and team are testing the effects of antibodies, called scFv, on a protein receptor, called P2X4, as a way to reverse pain behaviors. This potential therapeutic is part of a recent patent application that covers **non-opioid drugs, therapies, and pain management** to target the P2X family of receptors. Their work led to the formation of a biotech startup, NeuroChronix, which is developing non-opioid treatments for chronic pain. The availability of novel and effective non-opioid treatment alternatives will reduce clinicians' reliance on addictive therapeutics for chronic pain management.

***Pain and the Immune System: A Novel Therapeutic Approach***

*Richard Traub, Ph.D., University of Maryland, Baltimore*

Traub and his team are developing a chronic pain therapeutic that is non-addictive as opposed to widely used opioids. The therapeutic targets toll-like receptors, or proteins important for immune function, but when over stimulated lead to chronic pain. Current treatments targeting these proteins are effective for reducing pain but lead to a compromised immune system. To combat this, Traub's therapeutic binds to the toll-like receptor with reduced potency to block some, but not all, activity. It is expected that this therapeutic will **reduce pain while maintaining the individual's ability to fight infection**. Individual health and quality of life could improve for those living with chronic pain.

***Functional Restoration for Chronic Pain Management in Active-Duty Military Personnel: An Effectiveness-Implementation Trial***

*Alan Peterson, Ph.D., (left) University of Texas Health Science Center at San Antonio*

*Kate Comtois, Ph.D., M.P.H., (right) University of Washington*

Medically supervised pain management strategies that combine exercise, psychological counseling, and disability management, called functional restoration programs, are a **cost-effective means of managing chronic musculoskeletal pain**. This project seeks to create a standardized framework for training clinicians to implement one such program, called Functional and Occupational Rehabilitation for Troops, in military health care settings. The outcomes of the study are expected to lead to **improved health care delivery policies and practices** related to chronic musculoskeletal pain and quality of life for Service Members and their beneficiaries.

"I have been very privileged to participate in several of the CPMRP's reviews. I always look forward to the intellectual challenge of reading and determining the impact of research proposals for the military and for the entire pain community. The panel situation is very supportive where the scientists and other specialists go out of their way to ensure the consumer understands the technical aspects of the proposals. These reviews allow the voice of a person with pain to be recognized and heard as part of the review and funding process, as well as determine the future of research on chronic pain management. "

***Retired U.S. Air Force Lt. Col. Joseph "Tom" Norris, American Chronic Pain Association, Peer Reviewer, FY19-FY22***

# COMBAT READINESS – MEDICAL RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY19, the Combat Readiness – Medical Research Program (CRRP) supports research that may be deployed closer to the point of injury to support treatment of battlefield injuries and prevent death from potentially survivable injuries.

| *FY22 Congressional Appropriations* |
|---|
| **$10M** |
| *FY22 Research Investment* |
| Rapid Development and Translational Research Award .... $8,626,618 |
| Modification to ongoing awards ..... $207,547 |
| **Total:** $8,834,165 |
| *FY22 Withholds and Management Costs* |
| USAMRDC ..... $193,320 |
| SBIR/STTR ..... $334,000 |
| Mgt Costs (6.74%)..... $638,515 |
| **Total:** $1,165,835 |

## WHY IS THERE A NEED FOR RESEARCH ADDRESSING THE MEDICAL NEEDS OF WARFIGHTERS ON THE BATTLEFIELD?

**The future operational environment will require medical personnel to carefully manage resources in response to surges in casualties in dispersed locations over extended distances[1]**

**Over a 10-year period, ~1,000 U.S. military personnel could have been saved by innovations in battlefield trauma care[2]**

- The future operational environment will require non-medical personnel to conduct **more advanced medical care** than ever before[1]
- Addressing battlefield casualties as close to the point of injury as possible directly translates to **improved readiness and responsiveness** within the military
- The risk of death **significantly decreases** for combat casualties surviving greater than 4 hours post injury[3]

## HOW IS THE PROGRAM ADVANCING BATTLEFIELD MEDICINE?

In FY22, the CRRP established the following program priorities (left) and invested in four research areas (right) aligned to them.

- Wound Care Solutions for Complex Trauma and Tissue Regeneration
- Solutions to Enhance Combat Care Delivery Through the Far-Forward Environment
- Solutions to Enhance Warfighter Readiness

- Medicine and Therapy to Address Complex Trauma and Start Tissue Regeneration, $2,199,210
- Highly Infectious Disease Treatment and Transport, $3,165,055
- Extracorporeal Life Support, $1,999,548
- Ruggedized Oxygen Generation Systems, $2,990,937

[1] Army Futures Command. 2022. *Army Futures Command Concept for Medical 2028*. https://api.army.mil/e2/c/downloads/2022/04/25/ac4ef855/medical-concept-2028-final-unclas.pdf. | [2] Based on data collected from 2001-2011 in Eastridge BJ, et al. 2012. *Journal of Trauma and Acute Care Surgery* 73(6 Suppl. 5):S431-S437. | [3] Shackelford SA., del Junco DJ, et al. 2021. Case-control analysis of prehospital death and prolonged field care survival during recent US military combat operations. *Journal of Trauma and Acute Care Surgery* 91(2S): S186-S193 DOI: 10.1097/TA.0000000000003252.

**PROGRAM MISSION:** *Develop innovative high-impact solutions to increase medical readiness, diagnose and treat life threatening injuries, reduce morbidity and mortality, and promote positive long-term outcomes for the Warfighter*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**13 of 23 funded awards proposed regulatory filings with the FDA at or shortly following the conclusion of the period of performance**

**Burn Wound Treatment**

***Peptide Therapy to Limit Burn Conversion and Speed Wound Closure***

*Richard Clark, M.D., NeoMatrix Therapeutics*

This research is studying the use of a novel bioactive peptide, cNP8, for treating burn wounds. cNP8 works by promoting **tissue healing and regeneration** while limiting conversion of burn injuries to more serious wounds. The study resulted in a successful Investigational New Drug application filing, and the drug's developer, NeoMatrix, received approval from the FDA to proceed with phase 1 clinical trials. If successful, this project could lead to a therapy that mitigates the long-term effects of burn injuries.

**Self-Heating Packaging**

***Self-Heating Packaging for On-Demand Blood Product Warming***

*Arif Rahman, Ph.D., MaxQ Therapeutics, Inc.*

The MaxExo™ is a small, robust, and easy-to-use blood warmer that uses a chemical reaction rather than electricity to warm freeze-dried plasma. A research team from MaxQ Research, the MaxExo's manufacturer, met with military and civilian stakeholders to identify eight operational requirements to guide the development of the device for **use at trauma sites and on the battlefield**. The team is now in the process of testing chemical combinations capable of meeting those requirements so the device can be fielded to aid in the provision of medical treatment to Warfighters.

**Whole-Blood Surrogate**

***A Whole Blood Surrogate for Treating Acute Blood Loss***

*Michael Bruckman, Ph.D., Haima Therapeutics, LLC.*

This study focused on developing dried, whole blood substitutes that can be used as a supplement, or even as an alternative, to supplies of whole blood in austere battlefield environments. The team is collaborating with biotechnology companies to co-administer blood component surrogates already in development. The resulting treatment strategy will advance the delivery of both **front line care** in combat situations and **lifesaving interventions** during prolonged and en-route care in austere and combat environments, thus improving operational readiness.

"The CRRP continues to allow a pathway for end-users from the battlefield to pass along their experiences to those researchers looking towards the next conflict and bring innovation to those medical personnel that need it most."

***U.S. Army Master Sgt. Daniel McGarrah, Special Operations Command Central, Programmatic Panel Member FY22-FY23***

# DUCHENNE MUSCULAR DYSTROPHY RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY11, the Duchenne Muscular Dystrophy Research Program (DMDRP) supports the study of muscle and muscle regeneration and development of advanced technologies in stem cell and gene therapy methods to alleviate muscle weakness attributable to muscular dystrophy, as well as conducts clinical research relevant to muscle-related diseases with the goal of improving muscle structure and function.

| FY22 Congressional Appropriations | |
|---|---|
| **$10M** | |
| **FY22 Research Investment** | |
| Idea Development Award | $3,009,933 |
| Investigator Initiated Research Award | $71,063 |
| Translational Research Award | $6,139,048 |
| **Total:** | $9,220,044 |
| **FY22 Withholds and Management Costs** | |
| USAMRDC | $193,320 |
| SBIR/STTR | $334,000 |
| Mgt Costs (2.67%) | $252,636 |
| **Total:** | $779,956 |

"I feel fortunate to be part of DMDRP and have my voice heard by the researchers and doctors working toward better care and treatments for people living with Duchenne muscular dystrophy. I'm grateful that the research supported by the DMDRP encompasses all aspects of care and efforts toward a better understanding of the disease, and I'm especially excited about research toward a cure, as it's something I've prayed for and dreamt of for 18 years."

***Josh Argall, CureDuchenne, Peer Reviewer, FY21-FY22***

## WHY IS THERE A NEED FOR DUCHENNE MUSCULAR DYSTROPHY RESEARCH?

**~250,000** individuals worldwide are living with Duchenne muscular dystrophy[1]

Duchenne muscular dystrophy is **always** fatal[2]

Average life expectancy is **28 years**[3]

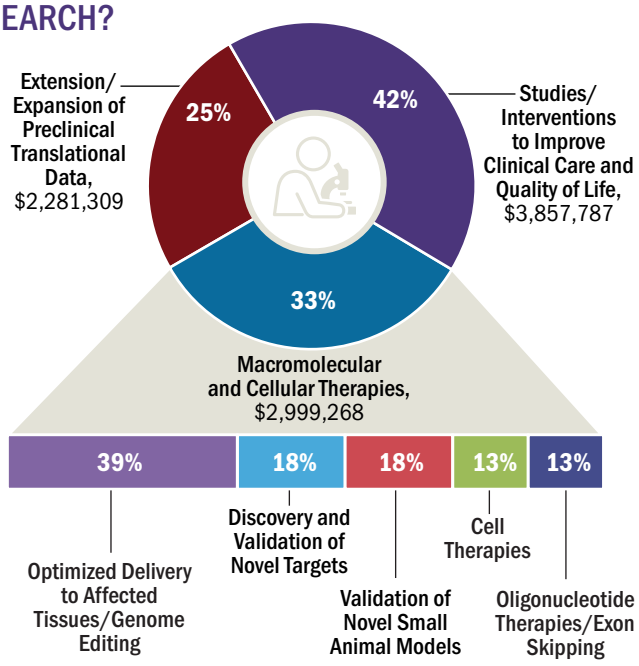
- For non-active duty recipients of the MHS in 2021, the **third** leading cause of medical encounters was musculoskeletal disease[4]
- Duchenne muscular dystrophy affects approximately **1** out of every **5,000** male infants with about **20,000** new cases each year[5]

Over a 7-year period[6] within the MHS, medical encounters for hereditary progressive muscular dystrophy for DOD beneficiaries included:

- **59,826** outpatient encounters
- **22,266** hospital bed days

## HOW IS THE PROGRAM ADVANCING DUCHENNE MUSCULAR DYSTROPHY RESEARCH?

The DMDRP directed FY22 investments into three program priorities. The Macromolecular and Cellular Therapies focus is further divided into five therapeutic development categories.




[1] Pfizer, Inc. 2023. Duchenne Muscular Dystrophy. https://www.pfizer.com/disease-and-conditions/duchenne-muscular-dystrophy. | [2] Duchenne Muscular Dystrophy. 2022. Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/23538-duchenne-muscular-dystrophy-dmd. | [3] Broomfield J, Hill M, et al. 2021. Life Expectancy in Duchenne Muscular Dystrophy: Reproduced Individual Patient Data Meta-Analysis. *Neurology* 97(23):e2304-e2314. | [4] *Medical Surveillance Monthly Report* Vol 29, No. 6, June 2021. | [5] Venugopal V, Pavlakis S. 2023. Duchenne Muscular Dystrophy *StatPearls (Internet)*. https://www.ncbi.nlm.nih.gov/books/NBK482346/. | [6] Based on a retrospective study conducted in 2020 with data from 2009-2015. | [7] Mázala DAG, Hindupur R, et al. 2023. Altered Muscle Niche Contributes to Myogenic Deficit in the D2- mdx Model of Severe DMD. *Cell Death Discovery* Jul 4;9(1):224.

**PROGRAM MISSION:** *To support discovery and development of therapeutics for Duchenne muscular dystrophy at all stages of the disease for the benefit of military Families and the general public*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Cellular Therapy**

***Pharmacological Regulation of Ion Channels***

*Foteini Mourkioti, Ph.D., University of Pennsylvania*

Duchenne muscular dystrophy is caused by mutations in the dystrophin protein that create a non-functional protein, which eventually turns into a stem cell disease that depletes stem cells in the muscles. Mourkioti's research found **activating a specific ion channel, called Piezo1,** which converts motor stimuli into nerve impulses, **can restore stem cell function in affected muscles**. This discovery suggests a **new approach for therapeutic intervention to treat the disease**.

**Gene Therapy**

***Gene Therapy for Duchenne Muscular Dystrophy***

*Dongsheng Duan, Ph.D., University of Missouri, Columbia*

Microdystrophin therapy, a type of gene therapy for Duchenne muscular dystrophy, can only partially restore heart function. Cardiomyopathy is the leading health threat associated with the disease. Duan's team demonstrated that increasing expression of a micro-peptide, called DWORF, in small animal models restored calcium equilibrium in cells that control heart contraction, reduced cardiac fibrosis, and improved overall heart function. **These results are paving the way for a potential combinatorial gene therapy for Duchenne cardiomyopathy**.

**Cellular Therapy**

***Targeting Immune Response to Allow Re-Administration of Gene Therapies***

*Melissa Spencer, Ph.D., University of California, Los Angeles*

Current gene replacement strategies for Duchenne muscular dystrophy rely on delivery using adeno-associated viral vectors, or AAV. Due to the body's immune response, re-administration of AAV is impossible. Spencer and her team sought to understand whether interfering with early immune events after initial gene delivery can allow re-administration of AAV-based therapies in the future. The team showed that **blocking classical complement, a part of the immune system, does not allow re-administration; however, blocking the responses of two types of immune cells, B-and T-cells, allowed for successful redosing** and subsequently increased dystrophin protein levels in their mouse models. These results **offer an avenue for safer and more effective re-administration of gene therapies**.

**Oligonucleotide Therapy**

***Antisense Oligonucleotide "Cocktail" for Improved Treatment***

*Jyoti Jaiswal, Ph.D., Children's Research Institute*

Antisense oligonucleotide, or ASO, therapies work by selectively binding to RNA regions responsible for Dystrophin protein production. Although promising, a key challenge is efficient and targeted delivery of this therapy. In a recent study, Jaiswal and his team uncovered that **aberrant dystrophic muscle stromal cell response contributes to poor myogenesis**. Targeting this deficit using an ASO cocktail reduced muscle loss and holds the potential to synergistically enhance ASO therapy.

**Improved Clinical Care**

***Clinical Utility of Serum Protein Biomarkers in Young Patients***

*Yetrib Hathout, Ph.D., New York State University, Binghamton*

Monitoring disease progression in very young Duchenne muscular dystrophy patients is challenging, resulting in delayed treatment and intervention. Hathout identified and validated a panel of **serum protein biomarkers for early muscle injury, inflammatory reaction, and response to corticosteroid treatment**. He is currently collaborating with two pharmaceutical companies to implement these assays in clinical trials funded outside of the CDMRP.

# EPILEPSY RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in 2015, the Epilepsy Research Program (ERP) funds research that expands understanding of the mechanisms by which brain injury produces epilepsy as well as research directed at the prevention of epilepsy and concomitant comorbidities in those known to be at high risk.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$12M** | |
| *FY22 Research Investment* | |
| Idea Development Award | $3,027,917 |
| Research Partnership Award | $3,899,572 |
| Virtual Post-Traumatic Epilepsy Research Center - Leadership Award | $1,951,124 |
| Virtual Post-Traumatic Epilepsy Research Center - Faculty Award | $1,495,381 |
| Modification to ongoing awards | $196,465 |
| **Total:** | $10,570,459 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $225,978 |
| SBIR/STTR | $400,000 |
| Mgt Costs (7.06%) | $803,563 |
| **Total:** | $1,429,541 |

"Serving as a consumer reviewer always brings me hope when I see the creativity and energy of the scientists that are working on creative solutions. The consumer voice is an integral part of the review process and I encourage others that would like to help join us in this effort."

***Matt Bolger, TSC Alliance, ERP Peer Review Consumer Reviewer, FY22***

## WHY IS THERE A NEED FOR EPILEPSY RESEARCH?

**Post-traumatic epilepsy is associated with a higher risk of death[1]**

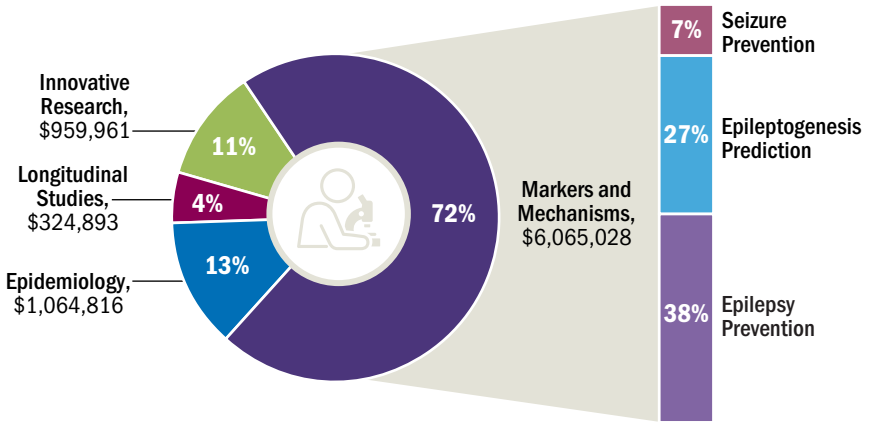
**The likelihood of developing post-traumatic epilepsy after TBI ranges from 2%-50%, depending on the severity and location of the injury[2]**

**Over a 22 year period, >450,000 Service Members reported a TBI[3]**

- **2,187** Iraq and Afghanistan War Veterans are affected by post-traumatic epilepsy[4]
- Among people aged 15 years and older hospitalized for a TBI, about **1 in 10** developed epilepsy in the following 3 years[5]
- In addition to seizures, post-traumatic epilepsy includes a spectrum of comorbid health conditions that impact quality of life[6]

## HOW IS THE PROGRAM ADVANCING EPILEPSY RESEARCH?

In FY22, the ERP invested across four program priorities pertaining to post-traumatic epilepsy. The Markers and Mechanisms priority is further divided into three sub-categories.




*Data do not include two awards which weren't required to address a program priority

[1] Karlander M, Ljungqvist J, et al. 2022. Risk and Cause of Death in Post-Traumatic Epilepsy: A Register-Based Retrospective Cohort Study. *Journal of Neurology* 269(11):6014-6020. | [2] Golub VM, Reddy DS. 2022. Post-Traumatic Epilepsy and Comorbidities: Advanced Models, Molecular Mechanisms, Biomarkers, and Novel Therapeutic Interventions. *Pharmacological Reviews* 74(2):387-438. | [3] Traumatic Brain Injury Center of Excellence. 2023. DOD TBI Worldwide Numbers. https://health.mil/Military-Health-Topics/Centers-of-Excellence/Traumatic-Brain-Injury-Center-of-Excellence/DOD-TBI-Worldwide-Numbers. | [4] Pugh MJ, Van Cott AC, et al. 2016. Epilepsy Among Iraq and Afghanistan War Veterans - United States, 2002-2015. *Morbidity and Mortality Weekly Report* 65(44):1224-1227. | [5] Ferguson PL, Smith GM, et al. 2010. A Population-Based Study of Risk of Epilepsy After Hospitalization for Traumatic Brain Injury. *Epilepsia* 51(5):891–898. | [6] Gugger JJ, Kennedy E, et al. 2022. Assessment in Post-9/11 Veterans with Epilepsy: Impact of Drug Resistance, Traumatic Brain Injury, and Comorbidity. *Neurology* 98(17):1761-1770.

**PROGRAM MISSION:** *To understand the mechanisms of post-traumatic epilepsy and associated comorbidities to improve quality of life, especially in Service Members, Veterans, and Caregivers*

## HOW IS THE PROGRAM MAKING AN IMPACT?

### POST-TRAUMATIC EPILEPSY CENTER WITHOUT WALLS

In FY22, the ERP initiated the Virtual Post-Traumatic Epilepsy Research Center, P-TERC, to enhance the quality and expand the quantity of research within the post-traumatic epilepsy field. Diaz-Arrastia and Pugh, two pioneers in the field, lead this effort. The ERP aims to expand capacity and foster mentorship and career development for established investigators looking to break into the post-traumatic epilepsy field as well as those early in their research career.

**Director and Deputy Director**

*Ramon Diaz-Arrastia, M.D., Ph.D.*, University of Pennsylvania

*Mary Jo Pugh, Ph.D., R.N.*, University of Utah

**Faculty**

*Chad Frasier, Ph.D.*, East Tennessee University

*Paul Koch, M.D.*, Virginia Commonwealth University

### *Detecting Epileptogenic Anatomical and Functional Brain Changes Due to TBI in Veterans*

*Anand Joshi, Ph.D., University of Southern California*

Joshi's team developed a data analysis toolbox that uses high-resolution anatomical and function MRI images to define regions and abnormalities in the brain after a TBI. The tool **can enable clinicians to map differences in a person's anatomic and neural connectivity** and may be useful for prediction of outcomes, including post-traumatic epilepsy. The development and implementation of innovative medical image analysis tools are critical for evidence-based **risk assessment of post-traumatic epilepsy risk after TBI**.

### *Acute Pharmacological Augmentation of Potassium Ion Channel Prevents Post-Traumatic Epilepsy and Chronic Traumatic Encephalopathy*

*Fabio Borges-Vigil, Ph.D., University of Texas, Health Science Center at San Antonio*

Borges-Vigil and his team published their first findings on the contribution of potassium channels, proteins that transport potassium ions across cellular membranes, in the development of post-traumatic epilepsy.[6] The study found mice treated with Retigabine, a potassium channel activator, experienced fewer post-traumatic seizures and decreased indicators associated with decline of brain health. Future studies by the research team will continue investigation of this FDA-approved drug as a **potential therapeutic for treating and preventing post-traumatic epilepsy.**

### *The Epidemiology of Epilepsy and TBI: Severity, Mechanism, and Outcomes*

*Mary Jo Pugh, Ph.D., R.N., South Texas Veterans Health Care System*

Pugh reported a participant-inspired modification to an ongoing ERP-funded investigation of connections between post-traumatic epilepsy, TBI, and health care outcomes in a post-9/11 Veteran population.[7] In March 2020, the study stopped due to the COVID-19 pandemic and interviews resumed in May of the same year. Observing the Veterans' desire to discuss the **impact of the COVID-19 pandemic on their health and daily lives**, Pugh expanded the study's scope to include these perceptions, data that otherwise would not have been collected. As a result, a **COVID-19-specific interview instrument is now included in a COVID-19 social science repository** hosted by the Social Interventions Research and Evaluation Network and is **freely available for use by the research community**.

[6] Vigil FA, Belchior H, et al. 2023. Acute Treatment with the M-Channel (Kv7, KCNQ) Opener Retigabine Reduces the Long-Term Effects of Repetitive Blast Traumatic Brain Injuries. *Neurotherapeutics* 20(3):853-869. | [7] Kalvesmaki AF, Gonzales E, et al. 2022. Post-9/11 Veterans Perceptions of the Pandemic: Areas of Greatest Impact on Health and Well-Being. *PEC Innovation* 100096.

# HEARING RESTORATION RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in 2017, the Hearing Restoration Research Program (HRRP) develops regenerative strategies and other options that may reduce the burden of hearing loss on Service Members.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$10M** | |
| *FY22 Research Investment* | |
| Focused Research Award - Funding Level 1 | $1,625,881 |
| Focused Research Award - Funding Level 2 | $7,250,961 |
| **Total:** | $8,876,842 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $158,197 |
| SBIR/STTR | $334,000 |
| Mgt Costs (6.64%) | $630,961 |
| **Total:** | $1,123,158 |

## WHY IS THERE A NEED FOR HEARING RESTORATION RESEARCH?

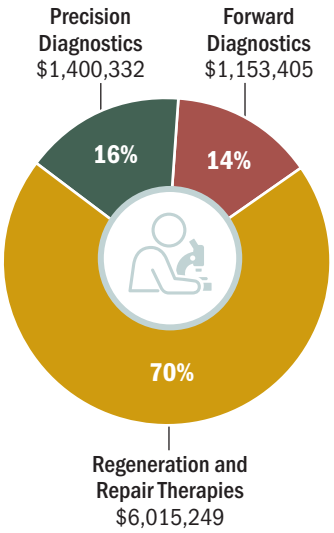

**Combat experience increases the risk of hearing loss by 63%**[1]

**In 2022, the Veterans Benefit Administration reported 1.4 million Veterans are affected by service-connected disability due to hearing loss**[2]

- **15%** of adults have some degree of hearing loss, however, those between 65-74 years old have a higher prevalence at 25%[3]
- **50%** of people 75 and older have hearing loss[3]

## HOW IS THE PROGRAM ADVANCING HEARING RESTORATION RESEARCH?

The HRRP directed FY22 investments into three intervention types (left) for research that address at least one of four program priorities (right).




**Translation of biological regeneration/repair mechanisms** into therapies that treat auditory system injury and restore auditory function

**Diagnostic tests** that help differentiate sensory, neural, synaptic, and central processing disorders may inform applicability and outcomes for current or future hearing restoration therapeutics

**Reliable in vitro human models** to facilitate the understanding, derivation, and characterization of human auditory cells, and/or to facilitate the evaluation of hearing restoration therapies

**Techniques/methods beyond the audiogram** to diagnose acute auditory system injury in austere or remote environments. For example, but not limited to, simple and rapid assessments that are compatible with portable platforms

[1] Wells TS, Seelig AD, et al. 2015. Hearing Loss Associated with U.S. Military Combat Deployment. *Noise Health* 17(74):34-42. | [2] U.S. Department of Veterans Affairs. 2023. *Veterans Benefits Administration Annual Benefits Report, Fiscal Year 2022.* https://www.benefits.va.gov/REPORTS/abr/docs/2022-abr.pdf. | [3] Quick Statistics About Hearing, The National Institute on Deafness and Other Communications Disorders, https://www.nidcd.nih.gov/health/statistics/quick-statistics-hearing#6. | [4] Jiang S, Welch P, et al. 2022. Mitigation of Hearing Damage After Repeated Blast Exposures in Animal Model of Chinchilla. *Journal of the Association for Research in Otolaryngology.* Oct;23(5):603-616. | [5] Jiang S, Sanders S, et al. 2023. Hearing Protection and Damage Mitigation in Chinchillas Exposed to Repeated Low-Intensity Blasts. *Hearing Research.* Mar 1;429:108703.

**PROGRAM MISSION:** *Deliver groundbreaking research and solutions for hearing restoration by advancing the understanding, diagnosis, repair, and regeneration of the auditory system*

## HOW IS THE PROGRAM MAKING AN IMPACT?

Building Collaboration

### HRF-NET

The HRRP founded the **Hearing Research Funders Network**, or HRF-Net, in 2022 to bring together federal, private, and international organizations funding auditory and vestibular research. **Forty participants** from **26 organizations** attended an inaugural meeting in January 2023 to discuss critical gaps in the field. To foster continuous exchange and collaboration, the HRRP hosts quarterly HRF-Net meetings. HRF-Net helps organizations align initiatives and create greater efficiencies in hearing research and development.

### *Repairing Cochlear Damage with Neurotrophin Therapy*

*Andrew Wise, Ph.D., The Bionics Institute of Australia*

Neurotrophins, proteins that regulate nervous system functions, are a promising therapeutic candidate to treat hearing loss because of their ability to stimulate the growth of sensory nerve cells and repair damaged synaptic connections. To work, however, they must be delivered into the inner ear over a sustained period of time in a manner that can be implemented clinically.

Through nanotechnology, Wise and his team developed a novel way to deliver neurotrophins by loading them in particles, called supraparticles. Experiments conducted in pre-clinical deafness models found neurotrophins delivered via supraparticles reached target cell populations and their presence sustained for at least one month after implantation and had a significant therapeutic effect. These results **advance the supraparticles-mediated neurotrophin delivery toward clinical translation**.

### *Therapeutic Function of Glucagonlike Peptide-1 for Hearing Restoration After Blast Exposure or Traumatic Brain Injury*

*Rong Gan, Ph.D., University of Oklahoma, Norman*

Repeated exposure to blast overpressure not only can result in traumatic brain injury but can also cause hearing problems, even when hearing protection is used. Gan and her team investigated the effectiveness of liraglutide, a medication that activates a specific protein receptor in the brain, called the glucagon-like peptide-1 receptor, in mitigating hearing damage. The team explored damage that was caused in laboratory animals exposed to repeated low-intensity blasts, similar to those experienced in combat environments that often result in mild TBI.[4] The team then treated animals with blast-induced hearing loss with liraglutide and found the medication significantly lowered their auditory brainstem response thresholds, the minimal intensity of sound required to hear,[5] resulting in improved hearing at lower sound intensity. They also found liraglutide treatment protective against blast-induced increase of neural activity in the auditory system, which could be a source of tinnitus, for animals wearing hearing protection. These results help **advance liraglutide as a potential treatment** for hearing loss and mild TBI after blast exposure.

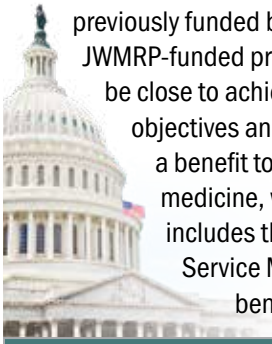
"Hearing loss is a global health concern, with the number of people with hearing loss expected to double by 2050 according to the World Health Organization. Any degree of hearing loss disrupts daily communication and affects people's ability to work, enjoy life, and stay active and not isolated. People use technology, strategies and medication, but there's a continued unmet need to treat hearing loss. While curative therapies are not yet available, the Hearing Restoration Research Program is working toward solutions that could restore or improve hearing, bringing a future of hope to those living with hearing loss."

***Barbara Kelley, Executive Director, Hearing Loss Association of America, Programmatic Panel Member, FY23***

# JOINT WARFIGHTER MEDICAL RESEARCH PROGRAM

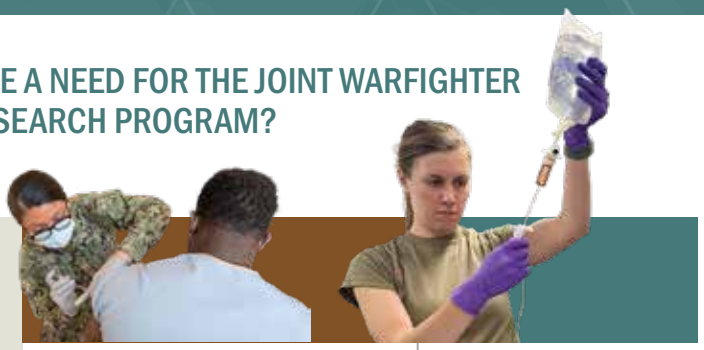
## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY12, Joint Warfighter Medical Research Program (JWMRP) funds are intented to augment and accelerate high-priority military medical priorities by supporting the advancement of projects previously funded by the DOD. JWMRP-funded projects should be close to achieving their objectives and yielding a benefit to military medicine, which includes the needs of Service Members and beneficiaries.



| *FY22 Congressional Appropriations* | |
|---|---|
| **$40M** | |
| *FY22 Research Investment* | |
| Military Medical Research and Development Award | $19,845,533 |
| Advanced Development Augmentation Funding | $14,500,000 |
| Modification to ongoing awards | $2,239,897 |
| **Total:** | $36,585,430 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $773,300 |
| SBIR/STTR | $1,335,000 |
| Mgt Costs (3.45%) | $1,306,270 |
| **Total:** | $3,414,570 |

## WHY IS THERE A NEED FOR THE JOINT WARFIGHTER MEDICAL RESEARCH PROGRAM?



**It can take 10-15 years to advance a drug from bench to beside**[1]

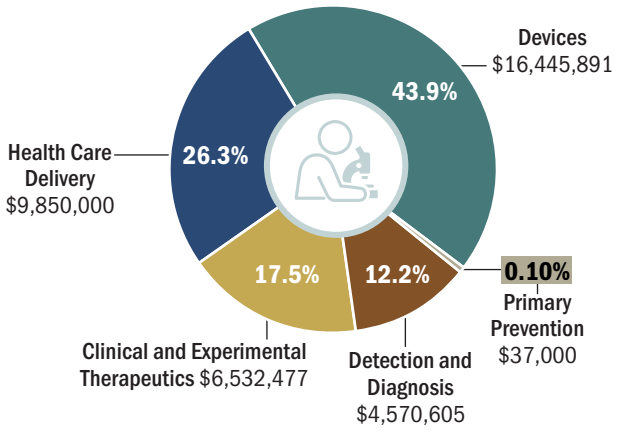
**Many technologies fail to cross the "valley of death," the gap between basic science and clinical practice where translational research is supported**

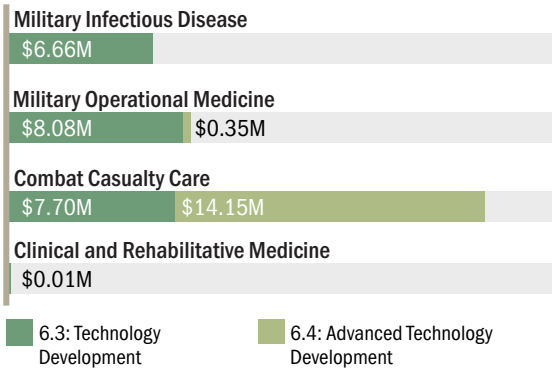
**There is an urgent need to support critical translational research to shorten the time for clinical implementation**

Military medicine not only promotes a medically ready force but also drives innovations in to civilian clinical practice,[2] benefiting beneficiaries and the American public

## HOW IS THE PROGRAM ADVANCING WARFIGHTER-SPECIFIC MEDICAL RESEARCH?

The JWMRP directed FY22 investments into five research types (left) aligned to three military-relevant areas of interest (right) for **technology development and advanced development and prototypes.**




[1] Cancer Research UK. 2022. How Long a New Drug Takes to Go Through Clinical Trials. https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/how-clinical-trials-are-planned-and-organised/how-long-it-takes-for-a-new-drug-to-go-through-clinical-trials. | [2] Hill, Lanessa. 2023. Researchers unite for warfighters at Combat Casualty Care conference. U.S. Army Medical Research and Development Command. https://mrdc.health.mil/index.cfm/media/articles/2010/ATACCC_Conference_2010.

**PROGRAM MISSION:** *Support the logical continuation of Department of Defense-funded research and development projects that augment and accelerate high-priority medical requirements to meet the needs of Service Members and other Military Health System beneficiaries*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Military Operational Medicine**

*Preclinical Development of a Novel Medical Device for Total Meniscus Reconstruction*

*Michael Dunn, Ph.D., Rutgers University*

Meniscal tears occur approximately 10 times more frequently among military personnel than in civilians, negatively affecting readiness and resilience and increasing cost of care. In collaboration with manufacturing and commercialization partner NovoPedics, Inc., Dunn's team optimized and validated small-sale production, packaging, and sterilization of **MeniscoFix™, a total meniscus replacement device** to **restore mobility and prevent onset of degenerative post-traumatic osteoarthritis**. MeniscoFix promotes tissue repair, remodeling, and maturation in response to biomechanical loading of the knee joint. Pending completion of FDA required pre-clinical and clinical testing, **MeniscoFix has the potential to accelerate return to duty, improve quality of life, and reduce long-term health costs.**

**Combat Casualty Care**

*Defining Oxygen Requirements for Combat Casualty Care*

*Adit Ginde, M.D., University of Colorado School of Medicine*

In combat casualty care, oxygen therapy is critical for preventing and treating complications caused by oxygen deficiency, called hypoxemia, but it poses a risk of causing damage from excess oxygen, called hyperoxemia. Expanding on a pilot trial funded by the Special Operations Command to define the oxygen requirements for critically injured patients, this research aims to measure the impact of normal oxygen levels, called normoxemia, on oxygen requirements and patient outcomes. In a completed **multi-center randomized trial of over 13,000 major trauma patients at eight trauma centers, the researchers developed an oxygen therapy protocol that successfully improved the number of days alive and off supplemental oxygen and number of days in the hospital, while reducing the amount of supplemental oxygen required to treat these patients**. This strategy has the potential to **positively impact resource planning** and supplemental oxygen use in combat.

**Military Infectious Diseases**

*Development of a Bacteria-Killing Therapeutic for Treating Staph Infections*

*Mina Pastagia, M.D., Armata Pharmaceuticals*

Antibiotic resistance and complicated bacterial infections make it a challenge to treat combat extremity wounds. This, in turn, negatively impacts operational readiness. This project is developing and evaluating **AP-SA02, a two-phage therapeutic cocktail that targets the bacteria Staphylococcus aureus, can penetrate biofilms, and can be combined with standard-of-care antibiotics**. Armata Pharmaceuticals, which produces AP-SA02, made it available for use in an ongoing clinical trial. Upon further clinical development and with FDA approval, this biologic alternative to antibiotics **can potentially save and improve lives and accelerate return to duty.**

"The research investments supported through the JWMRP deliver promising medical solutions that directly impact the health and readiness of our Warfighters. The program is guided by diverse stakeholders, representing the scientific and clinical communities and end users, who work together to understand where the most critical gaps are and ensure that the program is investing resources in those areas where we can have the greatest impact, whether it's in the clinic or on the battlefield."

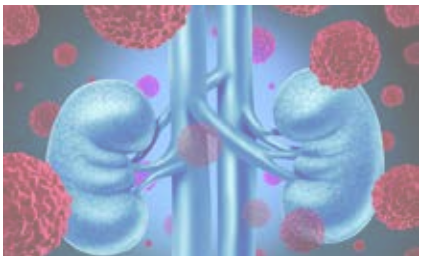
***U.S. Navy Capt. Tatana Olson, Defense Health Agency Research and Engineering Directorate, Programmatic Panel Member, FY22-FY23***

# KIDNEY CANCER RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY17, the Kidney Cancer Research Program (KCRP) promotes rigorous, innovative, high-impact collaborative research in kidney cancer for the benefit of Service Members, Veterans, and the American public.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$50M** | |
| *FY22 Research Investment* | |
| Academy of Kidney Cancer Investigators - Early Career Investigator Award | $3,254,428 |
| Clinical Trial Award | $2,064,247 |
| Concept Award | $1,986,243 |
| Idea Development Award - Early Career Investigator | $4,612,226 |
| Idea Development Award - Established Investigator | $17,224,799 |
| Nurse-Initiated Research Award | $564,000 |
| Postdoctoral and Clinical Fellowship Award | $1,284,547 |
| Translational Research Partnership Award | $7,404,273 |
| Modification to ongoing awards | $5,935,691 |
| **Total:** | $44,330,454 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $938,226 |
| SBIR/STTR | $1,669,000 |
| Mgt Costs (6.46%) | $3,062,320 |
| **Total:** | $5,669,546 |



## WHY IS THERE A NEED FOR KIDNEY CANCER RESEARCH?

**Renal cancer is the deadliest urological cancer with ~14,890 deaths expected in the U.S. population in 2023[1]**

**U.S. Marines and their Families stationed at Camp Lejeune, N.C., between 1975–1985 have a 35% higher risk of developing kidney cancer due to contaminated drinking water[2]**

**There is an increased risk of kidney cancer among Veterans that smoke cigarettes[3]**

- Incidence is **2X higher** in males than females[3]
- **Occupational exposures** during military service are linked to kidney cancer[1]
- Kidney cancer is **more common** in African American, Native American, and Alaska Native populations[3]

## HOW IS THE PROGRAM ADVANCING KIDNEY CANCER RESEARCH?

The KCRP directed FY22 investments into six program priorities.

Collaborate and partner with the next generation of researchers, $1,189,000

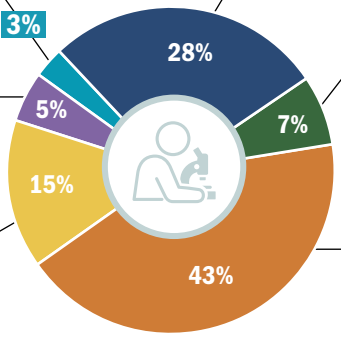
Conduct basic research into etiology and cancer progression, $10,312,883

Implement patient quality of life and survivorship strategies, $1,854,499

Define kidney cancer biology and develop treatments, $2,612,183

Develop screening, detection, and diagnostic strategies, $5,290,825

Develop novel therapeutic strategies and drug delivery systems, $16,945,992




[1] Key Statistics About Kidney Cancer. American Cancer Society. https://www.cancer.org/cancer/types/kidney-cancer/about/key-statistics.html. | [2] Bove FJ, Ruckart PZ, et al. 2014. Evaluation of Mortality Among Marines and Navy Personnel Exposed to Contaminated Drinking Water at USMC Base Camp Lejeune: A Retrospective Cohort Study. *Environmental Health* 13, 10. doi: org/10.1186/1476-069X-13-10. | [3] McLaughlin JK, Hrubec Z, et al. 1990. Renal Cancer and Cigarette Smoking in a 26-Year Followup of U.S. Veterans. *Public Health Reports* 105(5):535-537. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1580108/. | [4] Hu J, Tan P, et al. 2023. Tumor Heterogeneity in VHL Drives Metastasis in Clear Cell Renal Cell Carcinoma. *Signal Transduction and Targeted Therapy* 8:155. https://doi.org/10.1038/s41392-023-01362-2. | [5] Xu Y, Morales AJ, et al. 2022. Integrated TCR Repertoire Analysis and Single-Cell Transcriptomic Profiling of Tumor-Infiltrating T Cells in Renal Cell Carcinoma Identifies Shared and Tumor-Restricted Expanded Clones with Unique Phenotypes. *Frontiers in Oncology* 12:952252. https://doi.org/10.3389/fonc.2022.952252.

**PROGRAM MISSION:** *Advancing innovative and high-impact research to eliminate kidney cancer*

## HOW IS THE PROGRAM MAKING AN IMPACT?

***Identifying Drivers of Tumor Metastasis in Clear Cell Renal Cell Carcinoma***

*Lily Wu, M.D., Ph.D., University of California, Los Angeles*

To block the dissemination of renal cell carcinoma to the lungs, Dr. Wu and her team investigated the effects of an antibody targeting the protein, periostin. This protein triggers cell signals that promote tumor cell migration and escape into circulation. Wu's team found blocking periostin with an antibody significantly suppressed lung metastasis in a mouse model implanted with renal cell carcinoma. Her focus on understanding the fundamental mechanism of metastasis led to the discovery of the periostin-blocking strategy and other small molecule approaches that could be developed as **effective treatment for metastatic diseases**, including but not limited to clear cell renal cell carcinoma.

***A Novel Treatment Option for Patients with Clear Cell Kidney Cancer***

*Mei Yee Koh, Ph.D., Kuda Therapeutics, Inc.*

Koh and her research team created a **novel, first-in-class therapeutic**, KD061, that resulted in a **nearly 70% inhibition in tumor growth** and significant tumor cell death in laboratory mice during preliminary experiments. KD061 functions via a dual mechanism of inhibiting the hypoxia-inducible factors and inducing tumor cell death via ferroptosis, a novel form a death associated with iron-dependent lipid peroxidation. Oral administration of KD061 shows promise for future preclinical work and clinical trials for patients with kidney cancer and other tumor types that may be susceptible to iron-dependent cell death.

***Personalized Immunotherapy for Renal Cell Carcinoma***

*Shreeram Akilesh, M.D., Ph.D., University of Washington*

*Scott S. Tykodi, M.D., Ph. D., University of Washington*

Dr. Akilesh and Dr. Tykodi's team are addressing two understudied areas certain to impact future immunotherapy-based treatments for kidney cancer. First, their team created a fully-human "kidney cancer-on-a-chip" platform to study the interactions of a patient's immune cells with their tumor cells in 3D and in real-time. The chips provide an alternative to animal-based experiments, which are more time-consuming and costly and often not fully representative of human tumors. Second, they studied the unique biology of the blood vessels within kidney tumors,[5] which represent the essential entry point for a patient's immune cells to engage with the tumor. Together, **their discoveries could help scientists and clinicians better harness the power of the immune system to treat kidney cancer**.

"It's impossible to understate the impact KCRP and the research it funds is making for patients and their families. As a metastatic kidney cancer survivor and former clinical trial participant, I know firsthand that lives are saved by clinical research. KCRP's focus on funding research that allows doctors and scientists to ask bold questions that deserve answers provides crucial dollars that are often not available elsewhere. This program saves American lives every day by providing a funding mechanism for monumental research."

***Laura Esfeller, KCCure, Programmatic Panel Member, FY23***

# LUNG CANCER RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY09, the Lung Cancer Research Program (LCRP) funds research to identify, treat and manage lung cancer.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$20M** | |
| *FY22 Research Investment* | |
| Career Development Award | $1,179,003 |
| Concept Award | $1,804,971 |
| Idea Development Award | $10,131,520 |
| Investigator Initiated Translational Research Award | $4,781,877 |
| **Total:** | $17,897,371 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $386,660 |
| SBIR/STTR | $667,000 |
| Mgt Costs (5.54%) | $1,048,969 |
| **Total:** | $2,102,629 |

## WHY IS THERE A NEED FOR LUNG CANCER RESEARCH?

**Lung cancer is the leading cause of cancer mortality in the U.S., accounting for 22% of all cancer-related deaths[1]**

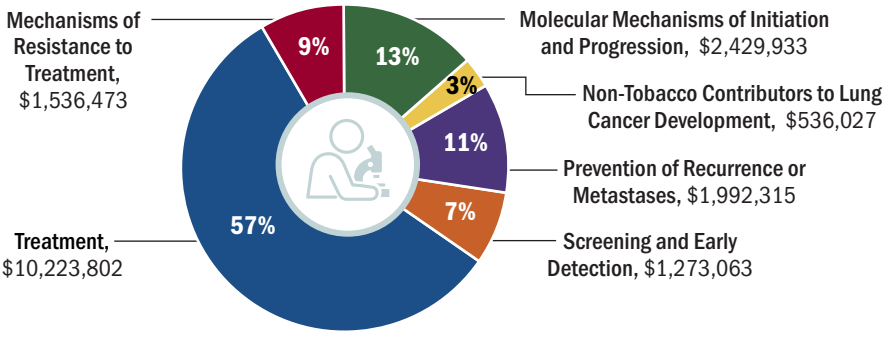
**~900,000**
**Veterans are at risk for lung cancer due to age, smoking, and other environmental exposures during and after military service[2]**

**~15 Veterans**
**die each day from lung cancer[3]**

- Lung cancer is the **3rd** most common cancer in the U.S.[4] with **>238,340** diagnoses and **>127,070** deaths in 2022[1]
- **10-15%** of all lung cancers occur in non-smokers[5]

## HOW IS THE PROGRAM ADVANCING LUNG CANCER RESEARCH?

The LCRP directed FY22 investments into six program priority areas.




"As a U.S. Navy Veteran and lung cancer researcher, I am honored to be part of the Programmatic Panel for the LCRP and impressed with the innovative and groundbreaking research that is funded. Importantly, these studies are singularly focused on positively impacting our Veterans, active-duty military, and the public by conducting clinically relevant research throughout the cancer care continuum, including early detection, risk assessment, diagnosis, treatment, disparities, and survivorship. This diverse funding portfolio is a testament to the community of scientists and physicians dedicated to eradicating this deadly disease and improving the lives for those afflicted by lung cancer."

***Matthew B. Schabath, Ph.D., H. Lee Moffitt Cancer Center and Research Institute, Programmatic Panel Member, FY16-FY23***

[1] Cancer Stat Facts: Common Cancer Sites. 2023. | [2] Odani S, Agaku IT, et al. 2018. Tobacco Product Use Among Military Veterans–United States, 2010-2015. *Morbidity and Mortality Weekly Report* 67:7-12. | [3] Moghanaki D and Hagan, M. 2020. Strategic Initiatives for Veterans with Lung Cancer. *Federal Practitioner* 37(Suppl 4): S76–S80. https://doi.org/10.12788/fp.0019. | [4] Centers for Disease Control and Prevention. 2023. *Lung Cancer Statistics*. https://www.cdc.gov/cancer/lung/statistics/index.htm. | [5] Lung Cancer Among People Who Never Smoked. 2023.

**PROGRAM MISSION:** *Support and integrate research from multiple disciplines for risk assessment, prevention, early detection, diagnosis, management, and treatment for the control and cure of lung cancer*

## HOW IS THE PROGRAM MAKING AN IMPACT?

### *Personalized Medicine for Small Cell Lung Cancer*

*Christopher Vakoc, M.D., Ph.D., Cold Spring Harbor Laboratory*

Dr. Vakoc and his team are investigating the molecular mechanisms of a **variant of small cell lung cancer** that initiates in lung sensory cells, called tufts cells. Their goal is to advance progress towards more tailored therapeutics. Early findings reveal **two previously undescribed proteins**, OCA-T1 and OCA-T2, can form a complex with a third protein, the transcription factor, POU2F3, within tuft cells.[6] These three proteins are critical for tuft cell identity and development of this cancer variant. This research provides insight into **markers and unique molecular vulnerabilities that could be leveraged for detection and/or development of therapeutics for tuft-cell derived small cell lung cancer**.

### *Using Biomarkers to Identify Immune Checkpoint-Based Therapies*

*Fumito Ito, M.D., Ph.D., Roswell Park Division Health Research Inc.*

Dr. Ito and his team identified a protein, CX3CR1, present in the blood T lymphocytes of those patients with non-small cell lung cancer who experienced long-term tumor shrinkage and cancer remission while undergoing chemoimmunotherapy.[7] This protein could be a **potential biomarker for identification of individuals with non-small cell lung cancer who are more likely to experience long-term benefits from chemoimmunotherapy**. These results indicate that a blood test for detection of CX3CR1 could be feasible for those with non-small cell lung cancer and other cancers and may improve patient outcomes, though additional research is needed.

### *Targeting Replication Stress Vulnerabilities in Small Cell Lung Cancer*

*Triparna Sen, Ph.D., Icahn School of Medicine at Mount Sinai*

Two primary issues related to low survival among patients with small-cell lung cancer are the lack of druggable targets and limited and short-lived response to immunotherapies. Proteins involved in cellular response to DNA damage are overexpressed in small-cell lung cancer, leading to a potential therapeutic target. Sen found **pairing immunotherapy with a drug regulating the overexpression of the DNA damage response protein, WEE1, enhanced the effects of immunotherapy in multiple small-cell lung cancer preclinical models**.[8] The team is now analyzing patient samples from a clinical trial testing a combination of chemoimmunotherapy and a drug that blocks DNA damage response to determine whether there is a clinical correlation.[9] If successful, this combination could be used in **current therapy guidelines and provide additional treatment options for small-cell lung cancer**. The team also identified novel mechanisms by which the DNA damage response proteins modulate the immune microenvironment paving the way for an improved understanding of this deadly disease.

"The LCRP provides unique opportunities for support of innovative and bold ideas to advance our understanding of lung cancer. As a panel member, I witness firsthand how funding diverse projects and investigators at different stages of their careers ensures the much-needed progress in reducing the burden of the disease on our military, their Families, and the general public."

***Konstantin H. Dragnev, M.D., Dartmouth-Hitchcock Norris Cotton Cancer Center, Programmatic Panel Member, FY15-FY23***

[6] Wu XS, He XY, et al. 2022. OCA-T1 and OCA-T2 Are Coactivators of POU2F3 in the Tuft Cell Lineage. *Nature* 607; 169–175. | [7] Abdelfatah E, Long MD, et al. 2023. Predictive and Prognostic Implications of Circulating CX3CR1+ CD8+ T cells in Non-Small Cell Lung Cancer Patients Treated with Chemo-Immunotherapy. *Cancer Research Communications*. Mar 30;3(3):510-520. https://doi.org/10.1158/2767-9764.CRC-22-0383. | [8] Taniguchi H, Caeser R, et al. 2022. WEE1 Inhibition Enhances the Antitumor Immune Response to PD-L1 Blockade by the Concomitant Activation of STING and STAT1 Pathways in SCLC. *Cell Reports* 39(7):110814. | [9] Sen T. 2023. STING Pathway Activation by Ataxia Telangiectasia and Rad3-Related Inhibition Potentiates Antitumor Immune Response to Anti-PD-L1 Antibody in Small Cell Lung Cancer. *Cancer Research* 83(7 supplement);2265.

# LUPUS RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

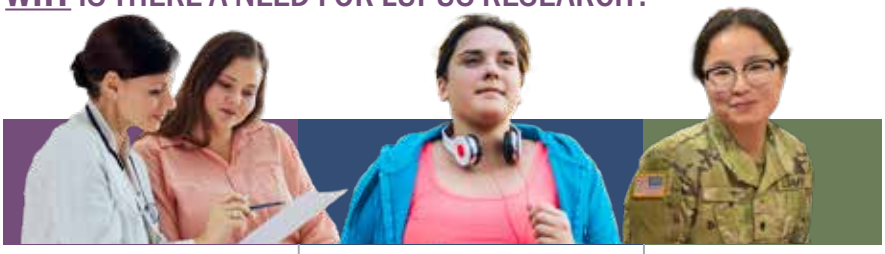
Established in 2017, the Lupus Research Program (LRP) supports innovative, high-risk, high-reward studies that offer the promise of shifting current paradigms with the hope of improving treatments and quality of life.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$10M** | |
| *FY22 Research Investment* | |
| Idea Award | $1,198,883 |
| Impact Award | $5,249,969 |
| Transformative Vision Award | $2,499,628 |
| **Total:** | $8,948,480 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $150,000 |
| SBIR/STTR | $334,000 |
| Mgt Costs (5.96%) | $567,520 |
| **Total:** | $1,051,520 |

"Participating in the first-ever Lupus Research Program for the DOD proved not only exhilarating but hopeful. What I came away with is that there is reason to believe that the 'cruel mystery' of lupus will be solved, and that by research, this devastating disease will no longer be misunderstood. Though irreversible lupus damage plagues my own life, I am immeasurably grateful to help our younger community look forward to quick diagnosis, appropriate medications, quality of life, a longer life expectancy, and maybe even the cure."

***Kyra Miller, Lupus Foundation of America, Consumer Peer Reviewer, FY17 and FY19***

## WHY IS THERE A NEED FOR LUPUS RESEARCH?



**Between ~161,000 to 1.5 million Americans are estimated to be living with lupus[1]**

**Lupus affects women at a rate ~10 times higher than men and is the 11th leading cause of death in females ages 25-44[2]**

**Similarly, female Service Members are 12.3X more likely to develop lupus compared to their male counter-parts[3]**

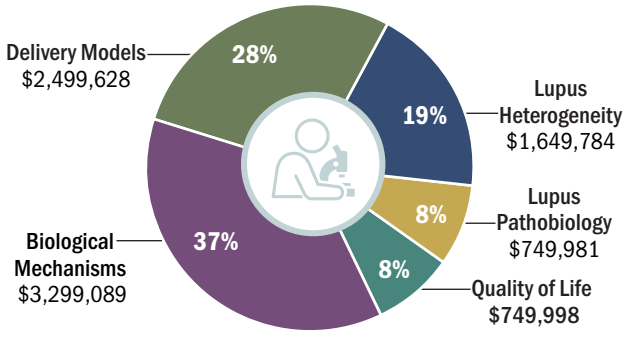
Minorities are at a **2-3X higher risk** of developing lupus[4]

Over a 10-year period within the MHS,[5] lupus medical encounters for Service Members and beneficiaries included:

- **67,372 patients**
- **705,352 out-patient encounters**
- **287,442 hospital bed days**

## HOW IS THE PROGRAM ADVANCING LUPUS RESEARCH?

The LRP directed FY22 investments into 10 focus areas.




[1] Sharif, Abdullah. 2021. New CDC Study Estimates 204,295 Americans Have Lupus - Lupus Research. *Lupus Research*. www.lupusresearch.org/new-cdc-study-estimates-204295-americans-have-lupus/. | [2] Yen E and Singh R. 2018. Brief Report: Lupus – An Unrecognized Leading Cause of Death in Young Females: A Population-Based Study Using Nationwide Death Certificates, 2000-2015. *Arthritis & Rheumatology* 70(8):1251-1255. https://doi.org/10.1002/art.40512. | [3] Denagamage P, Mabila S, McQuistan AA. 2023. Trends and Disparities in Systemic Lupus Erythematosus Incidence Among U.S. Active Component Service Members, 2000-2022. *Medical Surveillance Monthly Report* 30(12):2-5. | [4] Advancing Health Equity in Lupus. 2023. Lupus Foundation of America. | [5] Military Health System (MHS) Data from the Defense Medical Surveillance System, 2009-2018. 2020. The Armed Forces Health Surveillance Division, Defense Health Agency (DHA).

**PROGRAM MISSION:** *Fund research to understand, prevent, and diagnose lupus and to improve treatments and quality of life of patients, including Service Members, Veterans, and beneficiaries*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Machine Learning-Based Algorithms**

*Machine Learning to Quantify Adaptive Immunity for the Treatment of Lupus Nephritis*

*Marcus Clark, M.D., The University of Chicago*

Dr. Clark and his team developed **machine learning-based algorithms for characterizing the immune response** observed in lupus nephritis from images of kidney tissue samples.[6] After acquiring high-resolution images of cells, the team trained a machine learning neural network, known as Cell Distance Mapping 4, to accurately identify complex cell features and classify cells by type. Clark found specific **inflammatory markers within the kidneys associated with the progression towards end-stage renal disease and renal failure** that showed promise for **better predictors of progressive renal disease** and **potential new therapeutic targets**.

**Precision Medicine**

*Multi-Ancestral Genomic Approach to Precision Medicine*

*Carl Langefeld, Ph.D., Wake Forest University Health Sciences*

Epigenetic modifications to DNA, such as the addition of a methyl group onto DNA bases, can alter gene expression without changing the sequence of DNA. Langefeld and his team are investigating **epigenetic risk factors** for lupus to identify pathogenic mechanisms and therapeutics to target and treat the disease. Examining **genomic DNA from three pairs of female identical twins discordant for lupus**,[7] meaning only one twin is diagnosed with the disease, the researchers identified **59 areas of differentially methylated DNA** between the unaffected and affected twins, including 11 novel locations, representing potential risk factors for the disease. Analysis of these identified areas and FDA-approved drugs predicted interaction with 41 drugs, including one known lupus therapy. The team's findings **strongly suggest there are opportunities to repurpose already FDA-approved drugs as treatments** for lupus.

**Female-Biased Lupus Disease**

*Role for Abnormal Gene Expression from the Inactive X in Female-Biased Lupus Disease*

*Montserrat C. Anguera, Ph.D., University of Pennsylvania*

To prevent overexpression of certain genes, one X-chromosome is naturally silenced, or turned off, in those with two X-chromosomes, a process called X-chromosome inactivation. Anguera and her team explored how this inactivation is maintained within the silenced X-chromosome to **better understand the connection between sex and autoimmune disease** in lupus. The team used an **innovative single-cell profiling technology** to examine the genetic information of individual immune cells and detected high levels of impaired X-chromosome inactivation in B-cells, a type of white blood cell. Many genes that escaped X-chromosome inactivation in B-cells were immune regulatory genes, suggesting **nontypical gene silencing could lead to increased immune system activation in individuals with this disease,** and could explain a reason for **higher rates of autoimmune diseases, such as lupus, in women**. The team also assessed the impact of age on X-chromosome inactivation. In a recent publication,[8] the team reported genetic patterns correlated to patient age, but not necessarily to disease activity, indicating many of the genes affected by X-chromosome inactivation remain present despite disease remission.

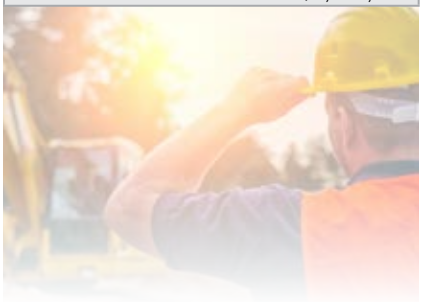
[6] Abraham R, Durkee MS, et al. 2022. Specific In Situ Inflammatory States Associate with Progression to Renal Failure in Lupus Nephritis. *The Journal of Clinical Investigation* 132(13):e155350. https://doi.org/10.1172/JCI155350. | [7] Marion MC, Ramos PS, et al. 2021. Nucleic Acid-Sensing and Interferon-Inducible Pathways Show Differential Methylation in MZ Twins Discordant for Lupus and Overexpression in Independent Lupus Samples: Implications for Pathogenic Mechanism and Drug Targeting. *Genes* 12(12):1898. | [8] Pyfrom S, Paneru B, et al. 2021. The Dynamic Epigenetic Regulation of the Inactive X Chromosome in Healthy Human B Cells Is Dysregulated in Lupus Patients. *Proceedings of the National Academy of Sciences of the United States of America* 118(24):e2024624118. https://doi.org/10.1073/pnas.2024624118.

# MELANOMA RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY19, the Melanoma Research Program (MRP) invests in research focusing on preventing melanoma initiation and progression for the benefit of Service Members, Veterans, their Families, and the American public.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$40M** | |
| *FY22 Research Investment* | |
| Focused Program Award - Rare Melanomas | $7,074,079 |
| Idea Award | $9,902,055 |
| Melanoma Academy Scholar Award | $2,659,399 |
| Mid-Career Accelerator Award | $3,603,657 |
| Team Science Award | $12,935,484 |
| **Total:** | $36,174,674 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $773,300 |
| SBIR/STTR | $1,335,000 |
| Mgt Costs (4.55%) | $1,717,026 |
| **Total:** | $3,825,326 |



[1] Skin Cancer (Including Melanoma) Health Professional Version. 2023. National Cancer Institute. | [2] Webber BJ, Tacke CD, et al. 2022. Cancer Incidence and Mortality Among Fighter Aviators in the United States Air Force. *Journal of Occupational and Environmental Medicine* 64(1):71-78. https://doi.org/10.1097/JOM.0000000000002353. | [3] Zullig LL, Sims KJ, et al. 2017. Cancer Incidence Among Patients of the U.S. Veterans Affairs Health Care System: 2010 Update. *Military Medicine* 182(7):e1883-e1891. doi: 10.7205/MILMED-D-16-00371. | [4] American Cancer Society. Survival Rates for Melanoma Skin Cancer. https://www.cancer.org/cancer/melanoma-skin-cancer/detection-diagnosis-staging/survival-rates-for-melanoma-skin-cancer-by-stage.html. | [5] Data provided by the Armed Forces Health Surveillance Division based on electronic records within the Defense Medical Surveillance System. Does not include care received outside the Military Health System.

## WHY IS THERE A NEED FOR MELANOMA RESEARCH?

**Invasive melanoma accounts for ~1% of skin cancers, but results in the most skin cancer deaths[1]**

**U.S. military aviators receive a melanoma diagnosis at an 87% higher rate as compared to a demographically similar U.S. population[2]**

**Melanoma is the 5th most common cancer among Veterans[3]**

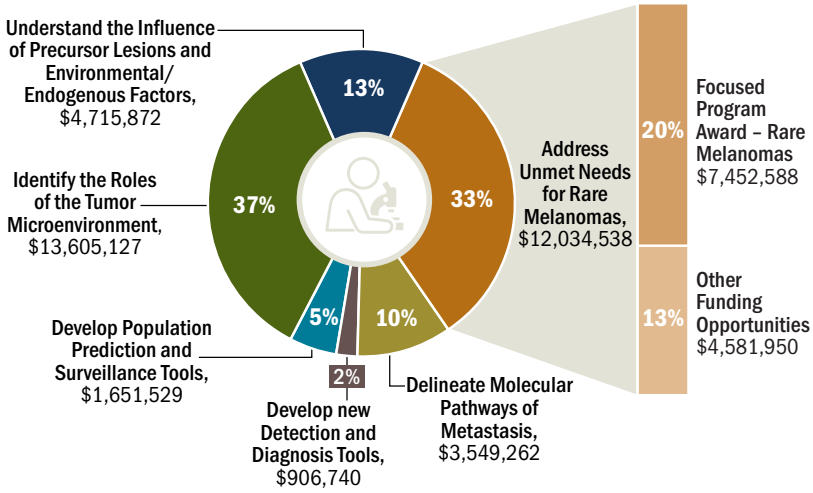
- When diagnosed as localized disease, the **5-year survival rate** for melanoma is **>99%** but decreases to **32%** when the disease spreads to other sites of the body[4]
- In 2022 in the U.S., there were an estimated **99,780** new cases and **7,650** deaths of melanoma

Over a 10-year period[5] in the MHS, melanoma medical encounters for Service Members included:

- **2,940 patients receiving care for malignant melanoma of the skin or eye cancer**
- **17,853 outpatient encounters**
- **1,111 hospital bed days**

## HOW IS THE PROGRAM ADVANCING MELANOMA RESEARCH?

The MRP directed FY22 investments into six program priorities emphasizing the role of prevention through the disease process and the need for addressing gaps in rare melanoma research.



**PROGRAM MISSION:** *To support development of earlier interventions to enhance mission readiness and diminish melanoma burden on Service Members, Veterans, their Families, and the American public*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Predicting Risk**



***Liquid Biopsy for Predicting Risk of Melanoma Recurrence***

*Helen Rizos, Ph.D., (left) Macquarie University*
*Georgina Long, M.B.B.S, Ph.D., (center) Melanoma Institute Australia*
*Elin Gray, Ph.D., (right) Edith Cowan University*

This multidisciplinary research team is developing better approaches to guide clinical care decisions for Stage II melanoma patients. They are using blood-based tests, known as liquid biopsies, **to detect biomarkers that will collectively indicate the continued presence of melanoma post-surgery**. If successful, this method can be used to **stratify patients with a high risk of recurrence** who would benefit from post-surgery treatments and may help in identifying those patients who have a low risk for recurrence and may not need additional treatments.

**Targeted Therapies**

***Overcoming Melanoma's Resistance to Targeted Therapies***

*Rhoda Alani, M.D., Boston University Medical Campus*

Most melanoma patients develop resistance to therapies about a year after treatment. Dr. Alani's team is testing the effectiveness of an epigenetic inhibitor, Corin, to **prevent targeted therapy resistance** in melanoma. This compound functions by blocking cellular processes that contribute to melanoma development and progression through non-mutational events. Additionally, the research team is **identifying biomarkers to predict patient response** to Corin and other epigenetic therapies in melanoma and **developing preclinical models to test the efficacy** of Corin in combination with targeted therapies to prevent drug resistance and promote cures for advanced disease.

**Novel Radiotherapy**

***Translational Studies for Targeted Alpha-Particle Therapy for Rare Melanomas***

*David Morse, Ph.D., H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida*

The study team, led by Morse, will conduct the first MRP-funded clinical trials for **a new, critically needed uveal melanoma treatment**. The objective of the first trial is to assess the efficacy of a multiple-injection regimen of radiation therapy that **utilizes alpha-particles to specifically target metastatic uveal melanoma cells**. During the second trial, the study team will test a **companion imaging agent** using three-dimensional internal radiation dosimetry, which will be used to monitor that sufficient therapeutic is getting to the tumor site.

"Over the years, I have used my policy background to advance causes, such as tanning bed legislation, and pushing for improved awareness regarding survivorship issues, such as exploring fertility considerations before starting any treatments. I feel that it is important to represent the patient voice, to dispel the notion that 'patients will do anything to live' and to stand up for quality of life issues. To other melanoma patients, I strongly encourage you to be your own health advocate and to go out and get involved. Your voice as a patient is important and it matters!"

***Jacqueline Smith, Melanoma Research Foundation, Consumer Reviewer, FY19-FY21***

# MILITARY BURN RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY11, the Military Burn Research Program (MBRP) addresses capability gaps in the treatment of combat-associated burn injuries and burn-injury complications.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$10M** | |
| *FY22 Research Investment* | |
| Clinical Translational Research Award | $4,436,001 |
| Idea Development Award | $211,015 |
| Technology/Therapeutic Development Award | $4,197,596 |
| Modification to ongoing awards | $266,739 |
| **Total:** | $9,111,351 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $200,000 |
| Mgt Costs (7.03%) | $688,649 |
| **Total:** | $888,649 |

## WHY IS THERE A NEED FOR MILITARY BURN RESEARCH?

**Compared with civilians, deployed Service Members are 2X as likely to suffer a burn injury[1]**

**The World Health Organization estimates 11 million burns occur annually, with an estimated 180,000 of those burns being fatal[2]**

**Burns constitute 10% of all combat-related injuries to the head and neck regions[1]**

- **5-20%** of all combat casualties suffered burn injuries during recent combat operations
- U.S. civilian emergency departments care for over **400,000** burn patients annually[3]
- **~40,000** patients require inpatient burn care annually in the U.S.[3]
- Nearly **10%** of hospitalized burn patients are considered severe, carrying a high risk of complications such as hypovolemia, sepsis, lung injury, and organ failure[4]
- **95%** of burn patients suffer from scarring, limitations in physical mobility, depression, anxiety, and PTSD

## HOW IS THE PROGRAM ADVANCING MILITARY BURN RESEARCH?

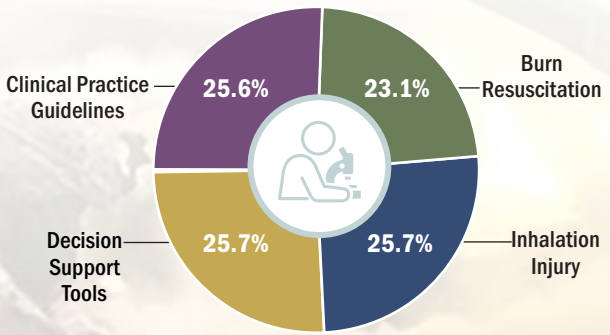
The MBRP focuses on atypical burns, mass casualty burn care, and burn-injury-related complications (left). The program directed FY22 investments toward four program priorities (right).

**Atypical Burns:** Exposure to cold, radiation, directed energy weapons, or high voltage/combat-related electrical injuries

**Burn Injury During Mass Casualty Incidents:** Incendiary device explosions, multi-passenger vehicle fires, etc.

**Burn-Injury-Related Complications:**

- Over/under fluid resuscitation to include limited or low volume resuscitation
- Acute respiratory distress syndrome
- Sepsis
- Inhalation injuries




[1] Engel CC, McBain RK, et al. 2020. The Effect of Blast-Related Burn Injuries from Prolonged Field Care to Rehabilitation and Resilience: A Review of the Scientific Literature. RAND Corporation. https://www.rand.org/pubs/research_reports/RRA807-1.html. | [2] World Health Organization. Burns. https://www.who.int/en/news-room/fact-sheets/detail/burns. | [3] https://ameriburn.org/who-we-are/media/burn-incidence-fact-sheet/. | [4] Heard J, Cronin L, et al. 2023. Massive Burn Injuries: Characteristics and Outcomes From a Single Institution. *Journal of Burn Care & Research*. 44(4):925-930. doi: 10.1093/jbcr/irac173.

**PROGRAM MISSION:** *Identify and close gaps in combat burn trauma care through military-focused research*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Wound Assessment**

***Portable Burn Wound Assessment Tool***

*Benjamin Levi, Ph.D. University of Texas Southwestern Medical Center at Dallas*

Levi and his team are validating a **portable, handheld, camera-based system** for evaluating burn injuries, called the Short Wave Assessment Tool, or SWAT. SWAT can be deployed and used at the point of care. The research team recently **developed a computer program suite for predicting burn depth in real time from high-resolution images**. With further development, SWAT may inform standardized assessment of burn care and treatment to improve healing of burn wounds and better long-term functional outcomes.

**Burn Treatment**

***Using Tranexamic Acid to Limit Burn Injury Severity***

*Damien Carter, M.D., F.A.C.S., Maine Medical Center*

Tranexamic acid is FDA-approved for prevention of hemorrhage in hemophilia patients and the treatment of heavy menstrual bleeding. It is already used in combat settings to treat hemorrhaging. Carter's team is evaluating the use of tranexamic acid as a means of **reducing burn wound progression and converting shallow burn wounds to deep wounds**. Preliminary results showed that tranexamic acid reduces inflammation and swelling in burn injuries and protects damaged cells. If successful, this therapeutic treatment could be **used in military and civilian settings with minimal training**, offering an alternative for burn treatment at the point of care in austere environments.

**Point of Injury Care**

***Enzymatic Debridement for Prolonged Field Care of Military Burn Wounds***

*Matthew Smiechowski, Ph.D., Guild BioSciences*

Following burn injury, removal of damaged or infected tissue, known as debridement, is a critical step in wound healing. Timing of debridement is important, since delays in this step of burn wound care can lead to poor burn recovery outcomes due to increased risk of infection and slower wound healing from the presence of dead tissue. Smiechowski's team is developing a nonsurgical burn wound debridement product suitable for use during prolonged field care. The product, called I-Debride™, is intended for **field application by first responders at the point of injury** and could be used by civilian paramedics and burn units. I-Debride is based on Guild BioSciences' ImmobiZyme™ technology, which combines a mixture of enzymes bound to a support matrix. Compared to other enzymatic debridement methods, I-Debride is shelf stable and does not require cold storage, allowing it to be carried in a medic bag. Other potential applications for I-Debride™ include **non-burn wounds such as diabetic wounds and pressure ulcers**.

"MBRP seeks out and funds research efforts to ensure our Warfighters deploy with simple and reliable tools to protect thermal injuries and minimize burn wound conversion in prolonged field care settings."

***Retired U.S. Marine Corps Lt. Col. Bryan Forney, Programmatic Panel Member, FY17-FY23***

"Burns are one of the most devastating injuries. Disfigurement, chronic pain, and the constant medical procedures can lead to depression, then suicidal ideation, which Service Members/Veterans are more likely to act on. Knowing that we can not only save lives, but also provide a better quality of life after injuries, is why I will continue to serve the burn community."

***Retired U.S. Army Staff Sgt. James West, Programmatic Panel Member, FY17-FY23***

# MULTIPLE SCLEROSIS RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY09, the Multiple Sclerosis Research Program (MSRP) supports innovative and impactful research that addresses fundamental issues and gaps in our knowledge of the disease in order to lessen its personal and societal impact.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$20M** | |
| *FY22 Research Investment* | |
| Clinical Trial Award | $6,078,476 |
| Early Investigator Research Award | $1,599,462 |
| Exploration - Hypothesis Development Award | $1,954,855 |
| Investigator-Initiated Research Award | $8,576,931 |
| **Total:** | $18,209,724 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $386,660 |
| SBIR/STTR | $667,000 |
| Mgt Costs (3.89%) | $736,616 |
| **Total:** | $1,790,276 |

"I have gained a lot of knowledge on my disease, and it has been interesting to see the evolution of applications from halting disease progression to reversing disease progression...I have a great amount of hope that the research being done towards finding a solution and eventual cure for multiple sclerosis are within reach."

***Izzy Abass, Paralyzed Veterans of America, Consumer Reviewer, FY22***

## WHY IS THERE A NEED FOR MULTIPLE SCLEROSIS RESEARCH?

**Multiple sclerosis impacts 1 million individuals in the U.S.**[1]

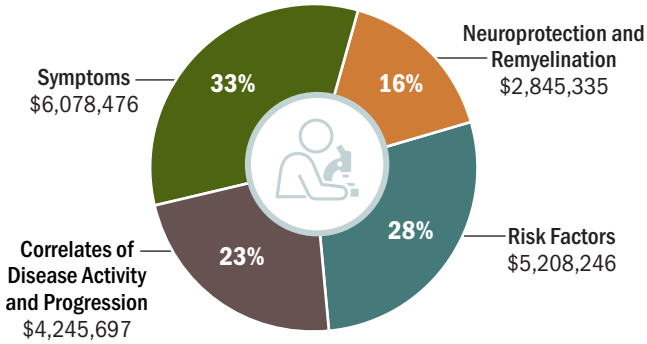
**The U.S. Armed Forces' incidence rate of multiple sclerosis is higher per 100,000 people compared to the general population; 12.9 versus 7.5, respectively**[2]

**The VA Multiple Sclerosis Centers of Excellence serve ~49,000 Veterans with the disease**[3]

- The annual economic burden of caring for people with multiple sclerosis in the U.S. is **$85.4 billion**[4]
- Clinical manifestations are diverse and often include motor deficit, visual loss, fatigue, and cognitive dysfunction
- The prevalence of multiple sclerosis within VA users increased from **141** per 100,000 Veterans in 1999 to **262** per 100,000 Veterans in 2014[5]
- Over a 10-year period[6] within the MHS, **>2,400** active-duty and reserve personnel received a new diagnosis of multiple sclerosis

## HOW IS THE PROGRAM ADVANCING MULTIPLE SCLEROSIS RESEARCH?

The MSRP directed FY22 investments into four program priorities.




[1] Wallin MT, Culpepper WJ, et al. 2019. The Prevalence of MS in the United States: A Population-Based Estimate Using Health Claims Data. *Neurology* 92(10):e1029-e1040. https://doi.org/10.1212/WNL.0000000000007035. | [2] Deussing EC, Jankosky CJ, et al. 2012. Estimated Incidence of Multiple Sclerosis Among United States Armed Forces Personnel Using the Defense Medical Surveillance System. *Military Medicine* 177(5):594-600. https://doi.org/10.7205/MILMED-D-11-00326. | [3] Cameron MH, Haselkorn JK, et al. 2020. The Multiple Sclerosis Centers of Excellence: A Model of Excellence in the VA. *Federal Practitioner* 37(Suppl 1):S6-S10. | [4] Bebo B, Cintina I, et al. 2022. The Economic Burden of Multiple Sclerosis in the United States: Estimate of Direct and Indirect Costs. *Neurology* 98(18):e1810-e1817. https://doi.org/10.1212/WNL.0000000000200150. | [5] https://n.neurology.org/content/92/10/e1029. | [6] Armed Forces Health Surveillance Division, Defense Health Agency. 2020. Military Health System Data from the Defense Medical Surveillance System, 2010-2019.

**PROGRAM MISSION:** *To support pioneering concepts and high-impact research relevant to the prevention, etiology, pathogenesis, assessment, treatment, and ultimate cure of multiple sclerosis for the benefit of Service Members, Veterans, and the American public*

## HOW IS THE PROGRAM MAKING AN IMPACT?

***Screening for Potential Drug Candidates in Multiple Sclerosis Lesions***
*Krystyn Van Vliet, Ph.D., Cornell University College of Engineering*
Therapies for stimulating remyelination, the reforming of the insulating layer around nerves, which prevents the loss of neurons, are used to treat multiple sclerosis. Van Vliet and her team developed Artificial Axons, a tool that uses **biocompatible polymers to mimic the behavior of natural nerve fibers**, also referred to as axons. The team explored whether physical changes in disease lesions, such as axon stiffness, diameter, and density, could inform the effectiveness of remyelination and drug response. The promising results of the study provided a screening platform and the proof-of-concept data for **developing therapeutics** for treating multiple sclerosis and the degeneration of neurons.

***Using Diffusion Tensor Imaging to Investigate Tremor Pathways in Multiple Sclerosis***
*John Lincoln, M.D., Ph.D., McGovern Medical School, University of Texas Health Science Center at Houston*
Dr. Lincoln's team used an imaging technique, called diffusion tensor imaging, **to explore how damaged nerve fiber tracts**, which are neural pathways between the brain and spinal cord, **contribute to disease-related tremors**. They identified five tracts with imaging features inversely correlated with tremor severity, of which three tracts showed strong positive correlation with tremor severity. These pathways offer **potential targetable sites for disease treatment**.

***Neural Mechanisms of Motor Fatigue in Multiple Sclerosis***
*Fay Horak, Ph.D., Oregon Health and Science University*
Horak and her team investigated the **neurological mechanisms and alterations contributing to motor fatigue**, as well as the effect of motor fatigue on balance. Their findings indicated that the connectivity between two brain regions crucial for movement, the cortex and the striatum, alongside alterations in cortico-cortical connectivity, may contribute to the development of motor fatigue in the disease. This insight is **an important step toward a better understanding of how motor fatigue works**.

***Examining the Effects of COVID-19 on Multiple Sclerosis***
*Sarah Lutz, Ph.D., University of Chicago*
COVID-19 and multiple sclerosis cause inflammation affecting the blood-brain barrier, or the protective layer on the inner surface of the brain's blood vessels, which filters out harmful substances. Lutz and her team are using mouse models to **investigate how both diseases affect a protein called VEGF**. VEGF plays an important role in the formation of new blood vessels. The ongoing study seeks to determine **whether COVID-19 infection exacerbates multiple sclerosis** and whether VEGF therapy provides an actionable biological link between the two diseases, potentially informing new treatment options.

***Real-World Clinical Trial of an Online Cognitive Behavioral Therapy for Managing Fatigue in Multiple Sclerosis***
*Robert McBurney, Ph.D, Accelerated Cure Project, Inc.*
McBurney's team aims to determine the real-world effectiveness of an **online cognitive behavioral therapy** program, called *Elevida*, for managing fatigue, the most common and disabling symptom of multiple sclerosis and for which there is no approved, effective treatment in the U.S. The large-scale trial, which will be conducted with FDA oversight, aims to include substantial numbers of participants from groups of people with the disease who are traditionally under-represented in clinical trials. The online therapy would be **accessible to people whose access to standard health care or providers, such as behavioral therapists, is restricted by their geographic location or disability**. The trial could lead to integration of *Elevida* with current treatments, improving the management of multiple sclerosis-related fatigue.

# NEUROFIBROMATOSIS RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY96, the Neurofibromatosis Research Program (NFRP) supports research into the diagnosis and treatment of neurofibromatosis and peripheral nerve sheath tumors to enhance the quality of life of Service Members, their Families, and all those affected by the disease.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$20M** | |
| *FY22 Research Investment* | |
| Early Investigator Research Award | $673,000 |
| Exploration - Hypothesis Development Award | $1,107,011 |
| Investigator - Initiated Research Award | $3,299,081 |
| New Investigator Award | $3,580,531 |
| Synergistic Idea Award | $9,219,440 |
| Modification to ongoing awards | $86,600 |
| **Total:** | $17,965,663 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $400,000 |
| Mgt Costs (8.34%) | $1,634,337 |
| **Total:** | $2,034,337 |

## WHY IS THERE A NEED FOR NEUROFIBROMATOSIS RESEARCH?

**~100,000**
**Americans are diagnosed with a neurofibromatosis disorder, which occurs in both sexes, all races, and ethnic groups[1]**

**Neurofibromatosis type 1 occurs in 1 in every 3,000 children born; type 2 occurs in 1 in every 25,000 people worldwide; schwannomatosis is believed to occur in 1 in every 40,000 people[2]**

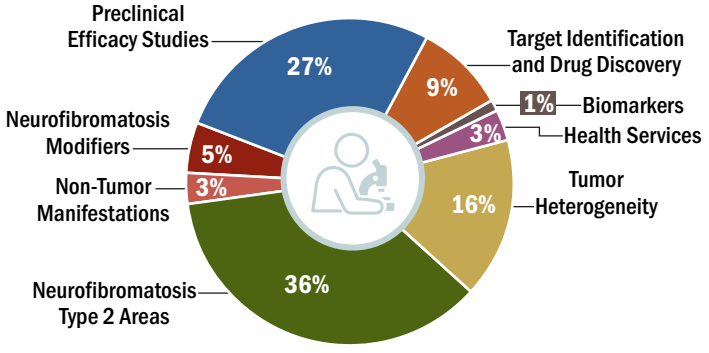
- **~50%** of people affected by neurofibromatosis type 1 don't exhibit family history of the disease[3]
- **1 out of every 3** people with neurofibromatosis type 1 live with abnormal skeletal growth, which can give rise to bone fractures and eventual limb amputation[4]

Over a 10-year period in the MHS,[5] neurofibromatosis medical encounters for Service Members and beneficiaries included:

- **6,609 patients**
- **48,491 outpatient encounters**
- **15,389 hospital bed days**

## HOW IS THE PROGRAM ADVANCING NEUROFIBROMATOSIS RESEARCH?

The NFRP directed FY22 investments into eight program priorities.




[1] Neurofibromatosis. The University of Texas MD Anderson Cancer Center. 2023 https://www.mdanderson.org/cancer-types/neurofibromatosis.html. | [2] Neurofibromatosis Clinics Association. 2023. https://nfpittsburgh.org/whatisnf/facts-statistics/. | [3] Neurofibromatosis 1. 2023. American Society of Clinical Oncology. https://www.cancer.net/cancer-types/neurofibromatosis-type-1. | [4] Military Benefit: Department of Defense NF Research Program. *Neurofibromatosis Network*. https://www.nfnetwork.org/nf-network-advocacy-program/military-benefit/. | [5] Military Health System (MHS) data from the Defense Medical Surveillance System, 2010-2019. The Armed Forces Health Surveillance Division, Defense Health Agency (DHA), Silver Spring, MD, November 2020. | [6] Plotkin SR, Allen J, et al. 2023. Multicenter, Prospective, Phase II Study of Maintenance Bevacizumab for Children and Adults with Neurofibromatosis Type 2-Related Schwannomatosis and Progressive Vestibular Schwannoma. *Neuro-Oncology* 25(8):1498-1506. http://doi.org/10.1093/neuonc/noad066. | [7] Chang LS, Oblinger JL, et al. 2021. Brigatinib Causes Tumor Shrinkage in Both NF2-Deficient Meningioma and Schwannoma Through Inhibition of Multiple Tyrosine Kinases But Not ALK. *PLOS One* 16(7). https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0252048. | [8] Cuevas-Navarro A, Rodriguez-Muñoz L, et al. 2022. Cross-Species Analysis of LZTR1 Loss-Of-Function Mutants Demonstrates Dependency to RIT1 Orthologs. *eLife*. 11:e76495. https://elifesciences.org/articles/76495.

**PROGRAM MISSION:** *Promote research directed toward the understanding, diagnosis, and treatment of neurofibromatosis type 1, neurofibromatosis type 2, and schwannomatosis to enhance the quality of life for persons with these disorders that impact Service Members, Veterans, and the general public*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Team Science**

***NFRP Neurofibromatosis Clinical Trials Consortium Award***

*Scott R. Plotkin, Ph.D., Massachusetts General Hospital*

Bilateral vestibular schwannomas, a hallmark of neurofibromatosis type 2-related schwannomatosis, are benign tumors of the nervous system, but can lead to deafness, imbalance, and other complications. This consortium successfully completed a **multi-center prospective study** of 22 participants to evaluate the safety, tolerance, and effectiveness of Bevacizumab, a targeted therapy to normalize blood vessels in tumors, in preventing the growth of these tumors and improving hearing.[6] The research team recently published results on extended maintenance therapy with low-dose Bevacizumab to minimize side effects. The study documented **high rates of hearing preservation and tumor stability during maintenance therapy**. Importantly, the team also showed treatment with Bevacizumab reduced distress related to tinnitus, ringing in the ears, and maintained overall quality of life for patients with neurofibromatosis type 2-related schwannomatosis.

**Combination Therapy**

***Novel Drug Combination for Treatment of Neurofibromatosis Type 2-Deficient Brain Tumors***

*Long-Sheng Chang, Ph.D., Research Institute at Nationwide Children's Hospital*

*Vijaya Ramesh, Ph.D., Massachusetts General Hospital*

Chang previously established a novel cell line modeling meningioma, one of the most common neurofibromatosis type 2-associated brain tumors. In this study, the research team evaluated the anti-tumor effects of the combination of Brigatinib, an FDA-approved drug for other indications, and INK128, a drug currently in clinical trials[7]. They found the **combination of the drugs improved anti-tumor effects**. The results of this study suggest the novel drug combination could lead to a treatment for meningiomas.

**Gene Identification**

***Molecular and Cellular Functions of LZTR1 Mutations in Schwannomatosis***

*Pau Castel, Ph.D., New York University School of Medicine*

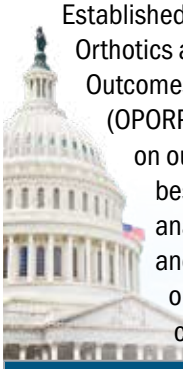
The least common form of neurofibromatosis is schwannomatosis, characterized by pain from benign tumor development along nerves. In those patients with schwannomatosis, mutations causing loss of functional LZTR1 protein are common. LZTR1 forms a complex with another protein, CRL3, which promotes signaling necessary for cell growth and immune function. Castel worked to understand the cellular and molecular effects of LZTR1 loss. In cells without LZTR1, the team found accumulation of two proteins, RIT1 and MRAS, which are normally degraded by the CRL3/LZTR1 complex. Additionally, to complete this work, the team developed a protocol for editing any gene in a schwann cell line. **This work made significant progress in unravelling the impact of LZTR1 in the development of schwannomatosis and generated a cell line that will be effective for future studies**.

"Participating in the NFRP peer review panel has been incredibly encouraging. To see firsthand the hard work, dedication, and care that these brilliant scientist and medical professionals are putting forth to find a cure and better treatments means more to me than I could ever describe. It has given me a whole new sense of hope. I am confident that, with the help of the NFRP, these professionals will have success in their research, and for that I am eternally grateful!"

***Laura Haslam, Neurofibromatosis Midwest, Consumer Peer Reviewer, FY21-FY22***

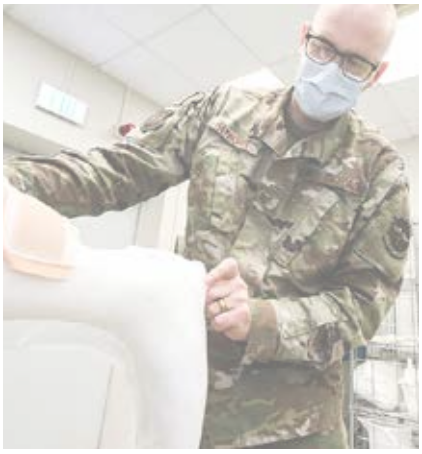
# ORTHOTICS AND PROSTHETICS OUTCOMES RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?



Established in FY14, the Orthotics and Prosthetics Outcomes Research Program (OPORP) supports research on outcomes-based best practices through analysis of prosthetic and/or orthotic device options that are clinically available.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$20M** | |
| *FY22 Research Investment* | |
| Clinical Research Award | $7,134,855 |
| Clinical Trial Award | $11,304,906 |
| **Total:** | $18,439,761 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $360,851 |
| SBIR/STTR | $667,000 |
| Mgt Costs (2.81%) | $532,388 |
| **Total:** | $1,560,239 |



[1] Limb Loss Statistics. Amputee Coalition. https://www.amputee-coalition.org/resources/limb-loss-statistics/. | [2] Extremity Trauma and Amputation Center of Excellence Registry (EACE-R) as of December 2020. | [3] Department of Veterans Affairs. 2021. VA Publishes Final Regulation to Improve Delivery of Prosthetic and Sensory Aids Services (press release). *VA News* Jan. 5. https://news.va.gov/press-room/va-publishes-final-regulation-to-improve-delivery-of-prosthetic-and-sensory-aids-services/. | [4] Stinner DJ, Burns TC, et al. 2010. Return to Duty Rate of Amputee Soldiers in the Current Conflicts in Afghanistan and Iraq. *The Journal of Trauma Injury, Infection, and Critical Care* 68(6):1476-9. https://doi.org/10.1097/TA.0b013e3181bb9a6c. | [5] American Orthotic and Prosthetic Association (AOPA) Fact Sheet; https://aopanet.org/media/fact-sheet/

## WHY IS THERE A NEED FOR ORTHOTICS AND PROSTHETICS OUTCOMES RESEARCH?

**Nearly 2 million Americans are living with limb loss[1]**

**1,727 military conflict-related amputations occured since 2001[2]**

**In 2020, more than 52% of Veterans treated at the VA received ~21 million prosthetic devices or items[3]**

- The number of amputees returning to active duty increased from 2.3% to 16.5% since the 1980's due to advancements in combat casualty care and amputee care[4]
- Every year, **~185,000** individuals in the U.S. will require a limb amputation[1]
- In 2016, Medicare approved payment for nearly 3.04 million orthotic codes that accounted for **>$1.0 billion** in Medicare expenditures[5]

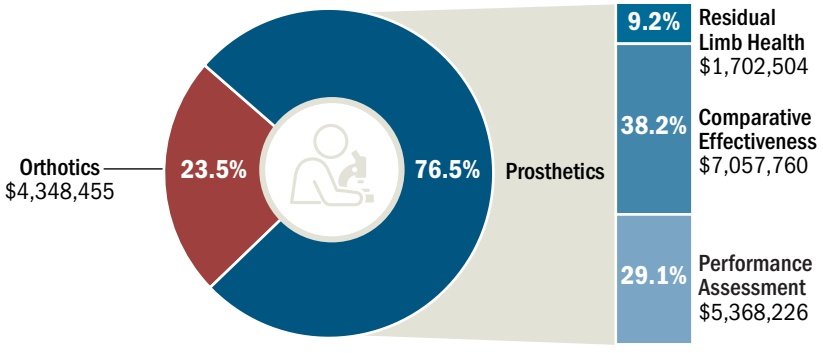
## HOW IS THE PROGRAM ADVANCING ORTHOTICS AND PROSTHETICS OUTCOMES RESEARCH?

The OPORP maintains three strategic goals (top) and directed FY22 investments into research addressing either orthotic or prosthetic outcomes (bottom). The prosthetics research area is further divided into three sub-categories.

Optimize patient-specific **TECHNOLOGY PRESCRIPTION**

Optimize patient-specific **REHABILITATION REGIMENS**

Support **STANDARDIZED ASSESSMENT** of patient outcomes related to prosthetics and orthotics



**PROGRAM MISSION:** *Advance orthotic and prosthetic research to optimize evidence-based care and clinical outcomes for Service Members, Veterans, and persons with limb loss and limb impairment*

## HOW IS THE PROGRAM MAKING AN IMPACT?

### Rehabilitation Strategies

***Hip Muscle Quality and Osseointegration Outcomes***

*Jeannie Bailey, Ph.D., and Richard O'Donnell, M.D., University of California, San Francisco*

Hip muscle quality is critical for lower limb amputees. The hip muscles of the residual limb often compensate for the loss of the amputated limb and support stability, balance, and endurance. To better understand the outcomes of available treatment options, Bailey and O'Donnell are investigating **how the hip muscles are affected in those undergoing two-stage transfemoral osseointegration surgery**. Preliminary data from their research suggest patients with an above-the-knee, osseointegrated limb appear to experience significantly worse hip muscle quality after osseointegration surgery. These data suggest **hip-strengthening rehabilitation strategies could be an integral component of the clinical care strategy for all patients with lower limb amputations**.

### Improving Quality of Life

***Assessing the Physical and Psychosocial Needs of Women with Limb Loss***

*Roxanne Disla, Ph.D., VA New York Harbor Health Care System*

To address the lack of data on female amputees, Disla and her team conducted **a national exploratory needs assessment to determine the unique physical and psychosocial needs of women with limb loss**. A preliminary analysis of the data collected revealed women with limb loss reported worse residual limb health, significantly fewer activity restrictions, and less satisfaction with appearance compared to men. They also reported less ease in social situations, higher anxiety and depression, and worse body image perception. Results from the study will be disseminated by the research team for immediate use in VA, DOD, and private clinics to **enable more evidence-based prescription of service and influence clinical practice guidelines**, leading to improved quality of life for women living with limb loss.

"I believe that merging the prosthesis user, researcher, and advocate perspectives is critical for making informed decisions about what paths are most likely to create meaningful and widespread advancements in orthotics and prosthetics care."

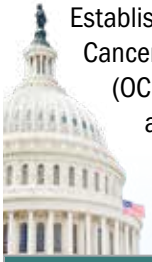
***Susannah Engdahl, M.D., American Orthotic and Prosthetic Association, Programmatic Panel Member, FY22-FY23***

"Knowing this funding exists and knowing teams of brilliant people are working hard to improve the lives of those injured in the line of duty fills me with happiness. Our sacrifices weren't forgotten."

***Retired U.S. Army Pfc. Tristan Wyatt, Programmatic Panel Member, FY18-FY23***

# OVARIAN CANCER RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?



Established in FY97, the Ovarian Cancer Research Program (OCRP) aims to define and address the critical research gaps facing the ovarian cancer community.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$45M** | |
| *FY22 Research Investment* | |
| Clinical Trial Award | $4,112,694 |
| Investigator-Initiated Research Award | $22,025,838 |
| Ovarian Cancer Academy - Early-Career Investigator Award | $4,273,682 |
| Pilot Award | $5,422,706 |
| Teal Expansion Award | $4,114,488 |
| Modification to ongoing awards | $423,209 |
| **Total:** | $40,372,617 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $862,946 |
| SBIR/STTR | $1,501,000 |
| Mgt Costs (5.31%) | $2,263,437 |
| **Total:** | $4,627,383 |

## WHY IS THERE A NEED FOR OVARIAN CANCER RESEARCH?

**In the U.S., ovarian cancer is the 5th leading cause of cancer-related deaths in women**[1]

**Ovarian cancer accounted for 20,433 cases among Service Members and beneficiaries in the MHS over a 10-year period**[2]

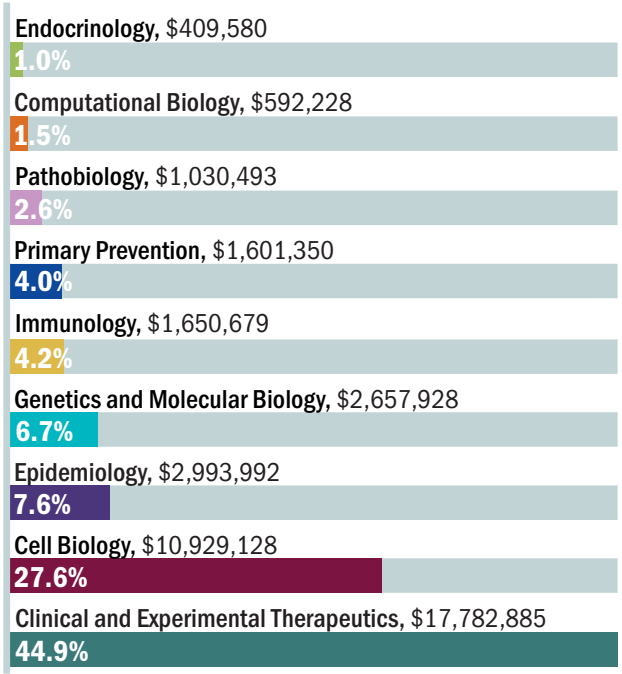
**17% of the active-duty population are female**[3]

- In the U.S., **~19,710** new diagnoses and **~13,270** deaths from ovarian cancer are estimated in 2023[4]
- The **5-** and **10-year** relative survival rates are **50%** and **38%**, respectively[5]

## HOW IS THE PROGRAM ADVANCING OVARIAN CANCER RESEARCH?

The OCRP identified six program priorities (left) and directed FY22 investments into 10 types of research (right) to address them.

- Understand the basic biology and etiology of ovarian cancer initiation, progression, metastasis, recurrence, genetics, and other critical events
- Develop novel therapeutic strategies for treatment and prevention
- Identify and develop new strategies for screening, early-stage detection, prevention, accurate diagnosis, and prognosis
- Identify and implement strategies to improve the survivorship and quality of life
- Address health disparities
- Improve precision medicine




[1] American Cancer Society. 2023. Key Statistics for Ovarian Cancer. https://www.cancer.org/cancer/types/ovarian-cancer/about/key-statistics.html. | [2] Military Health System (MHS) data from the Defense Medical Surveillance System, 2010-2019. 2020. The Armed Forces Health Surveillance Division, Defense Health Agency. | [3] Department of Defense. 2022. n.d. Department of Defense Releases Annual Demographics Report – Upward Trend in Number of Women Serving Continues. https://www.defense.gov/News/Releases/Release/Article/3246268/department-of-defense-releases-annual-demographics-report-upward-trend-in-numbe/. | [4] Key Statistics for Ovarian Cancer, American Cancer Society. 2023. https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.html. | [5] National Cancer Institute. Surveillance, Epidemiology, and End Results Program. 2023. https://seer.cancer.gov/statfacts/html/ovary.html. | [6] Garsed D, Pandey A, et al. 2022. The Genomic and Immune Landscape of Long-Term Survivors of High-Grade Serous Ovarian Cancer. *Nature Genetics* 52(12):1853-1854. https://doi.org/10.1038/s41588-022-01230-9.

**PROGRAM MISSION:** *To support patient-centered research to prevent, detect, treat, and cure ovarian cancer to enhance the health and well-being of Service Members, Veterans, retirees, their Family members, and all women impacted by this disease*

## HOW IS THE PROGRAM MAKING AN IMPACT?

### OVARIAN CANCER ACADEMY

The OCRP-funded Ovarian Cancer Academy brings together a group of talented and highly committed early-career investigators with their mentors and academy leadership in a synergistic partnership to establish the investigators as the next generation of ovarian cancer researchers.

**Academy Facts**

**21** Graduates

**14** Current Members

**995** Publications, **13** Patents, and **260** Funding Grants worth **>$100M** since 2009

*Highlight From The Academy*

***DNA Repair Genes and Genome Instability Early in High-Grade Serious Ovarian Cancer: Role of Antioxidants***

*Sophia George, Ph.D., University of Coral Gables, Miami*

As part of the Ovarian Cancer Academy, George identified heritable mutations that affect the expression of antioxidant gene associated with pre-cancerous and early cancerous lesions in the fallopian tube epithelium. Along with her research, George is engaged in various leadership and mentorship activities, including her role as an international research mentor in Nigeria and in the World Health Organization, Global Breast Cancer Initiative, Partnership Working Group. George is particularly interested in hereditary and racial disparities in ovarian cancer outcomes.

***Multidisciplinary Ovarian Cancer Outcomes Group***

*Malcolm Pike, Ph.D., Sloan Kettering Institute for Cancer Research*

Pike and his team in the Multidisciplinary Ovarian Cancer Outcomes Group, an international collaboration among researchers, clinicians, and patient advocates, are evaluating **molecular, genetic, clinical, personal, and lifestyle factors** as contributors to **exceptional long-term survival in patients** with advanced-stage high-grade serous ovarian cancer, the most common and lethal ovarian cancer. As part of this research, the Group analyzed 60 long-term survivors using whole-genome sequencing, transcriptome and methylome profiling of their primary tumor samples, comparing these data to that from 66 short- or moderate-term survivors.[8] Results associated with long-term survival included specific combinations of germline and somatic gene alterations, tumor cell phenotypes, higher neoantigen load, and differential immune responses. Patients who had the longest survival prominently displayed active B cell responses, and together with the rising interest in antibody drug conjugates, this suggests that **elite antibodies from long term survivors may provide novel therapeutic opportunities**.

***Optical Imaging Falloposcope for Early Ovarian Cancer Detection***

*Jennifer Barton, Ph.D., University of Arizona-Tucson*

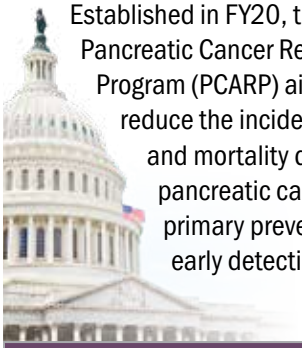
Late diagnosis is a central problem in ovarian cancer due in part to the lack of symptoms in early stages of the disease. Barton and her team developed **a portable falloposcope imaging system for detection of ovarian cancer in fallopian tubes.** The team is now conducting clinical testing to further develop the falloposcope device and prepare it for the operating theater. Ovarian cancer commonly originates in the fallopian tube and remains undetected until it metastasizes to the ovaries; **reliable falloposcope technology will enable for earlier detection and better prognoses** for ovarian cancer patients.

"I am honored to serve as a reviewer for the OCRP. As an ovarian cancer survivor and patient advocate, I'm proud to play a small part in the advancement of research and drug development."

***Kimberly Richardson, Ovarian Cancer Research Alliance, Ad-Hoc Programmatic Reviewer, FY22-FY23***

# PANCREATIC CANCER RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?



Established in FY20, the Pancreatic Cancer Research Program (PCARP) aims to reduce the incidence and mortality due to pancreatic cancer by primary prevention and early detection.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$15M** | |
| *FY22 Research Investment* | |
| Idea Development Award | $8,326,417 |
| Translational Research Partnership Award | $5,026,236 |
| **Total:** | $13,352,653 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $289,980 |
| SBIR/STTR | $501,000 |
| Mgt Costs (6.03%) | $856,367 |
| **Total:** | $1,647,347 |

"As the first federal research program completely dedicated to pancreatic cancer, the ability to evaluate research priorities each year provides timely support for gap-filling, innovative projects with significant potential to improve and extend the lives of patients. Scientists and patient advocates working side-by-side on the yearly evaluations only strengthens the potential for high-impact advances."

***Lynn Matrisian, Pancreatic Cancer Action Network, Consumer Reviewer, FY20-FY23***

## WHY IS THERE A NEED FOR PANCREATIC CANCER RESEARCH?

**Pancreatic cancer is the 3rd leading cause of cancer death in the U.S., with over 50,000 estimated to die in 2023 alone**[1]

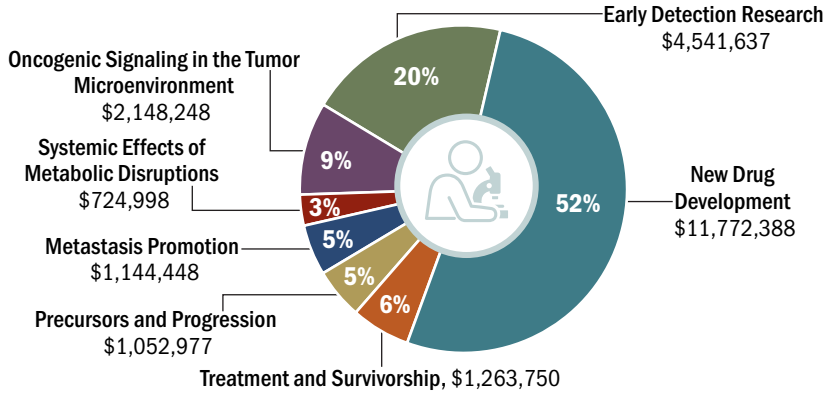
**Over a 10-year period,**[2] **>26,000 Service Members and beneficiaries in the MHS received care for pancreatic cancer**

**Over the same 10-year period, 200 active duty military members and more than 14,000 Veterans received a diagnosis**

- In 2023, **64,050** Americans are estimated to be diagnosed with pancreatic cancer[1]
- Smoking, weight, history of diabetes or chronic pancreatitis, chemical exposure, and family history are risk factors for pancreatic cancer[3]

## HOW IS THE PROGRAM ADVANCING PANCREATIC CANCER RESEARCH?

The PCARP directed FY22 investments into seven program priorities (top) aligned to the program's strategic goals (bottom).




**EXPAND** expertise by bridging diverse scientific fields

**FILL GAPS** and advance knowledge to drive new and innovative clinical trials

**FACILITATE** a multidisciplinary approach to advancing scientific knowledge

**RECRUIT** and **RETAIN** young investigators

**PROGRAM MISSION:** *Promote rigorous, innovative, high-impact research that leads to earlier pancreatic cancer diagnosis, new therapeutic tools, and improved outcomes*

## HOW IS THE PROGRAM MAKING AN IMPACT?

### *Association of Lipid and Metabolite Profiles with Pancreatic Cancer Risk*

*Rachael Solomon, Ph.D., National Cancer Institute*

Excessive alcohol use, family history, and diabetes increase the risk of pancreatic ductal adenocarcinoma, the most common form of pancreatic cancer.[3] Solomon's team assessed the association between metabolites, or small molecules involved in metabolism, and lipids, with pancreatic cancer risk. The research team evaluated blood samples collected as part of the NIH-sponsored Women's Health Initiative, a long-term health study focused on strategies for preventing various chronic diseases in women. The blood of participants who received a pancreatic cancer diagnosis years later included specific metabolites and lipids not detected in the blood of participants who did not develop pancreatic cancer. The metabolites and lipids identified, in combination with known pancreatic cancer risk factors, may **allow for earlier detection of disease and identification of groups of individuals at high risk for pancreatic cancer**.

### *Remote Malnutrition Monitoring After Pancreatectomy*

*Kea Turner, Ph.D., H. Lee Moffit Cancer Center and Research Institute, University of South Florida*

The increased risk of malnutrition following pancreatic surgery can make the recovery process long and challenging.[4] With **no interventions to address post-surgical malnutrition**, Turner and her team previously developed the Support Through Remote Observation and Nutrition Guidance, or STRONG, intervention, which provides nutritional counseling and uses a smartphone app to track food intake for people undergoing partial or complete removal of the pancreas. With evidence of the intervention's success, the team is now comparing STRONG against the current standard of care to gauge whether it leads to improved nutritional health and surgical recovery. If successful, STRONG will provide **at-home support to people after a pancreatectomy, so they can manage their nutritional needs**.

**Focused Pilot Research Award**

The PCARP released the Focused Pilot Research Award in FY23 to support the exploration and development of impactful and innovative concepts to advance supportive care interventions and reduce barriers to the implementation of health care. The program's objective for this award mechanism is to leverage and solicit rigorous and high-impact studies to improve patient reported outcomes, quality of life, and survivorship in a targeted and consistent manner.

[1] Pancreatic Cancer — Cancer Stat Facts, https://seer.cancer.gov/statfacts/html/pancreas.html. | [2] Military Health System (MHS) data from the Defense Medical Surveillance System, 2010-2019. The Armed Forces Health Surveillance Division, Defense Health Agency, Silver Spring, MD, November 2020. | [3] Pancreatic Cancer Action Network. 2023. Pancreatic Cancer Risk Factors. https://pancan.org/facing-pancreatic-cancer/about-pancreatic-cancer/risk-factors/. | [4] La Torre, M, Ziparo V, et al. 2013. Malnutrition and pancreatic surgery: prevalence and outcomes. *Journal of Surgical Oncology*. 107(7):702-8. doi:10.1002/jso.23304.

# PARKINSON'S RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

In FY22, Congress transitioned the Neurotoxin Exposure Treatment Parkinson's Program (NETP) to the Parkinson's Research Program (PRP) and broadened the research to all types of Parkinson's disease research.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$16M** | |
| *FY22 Research Investment* | |
| Early Investigator Research Award | $1,508,104 |
| Investigator-Initiated Research Award | $4,798,510 |
| Synergistic Idea Award | $8,977,810 |
| **Total:** | $15,284,424 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $320,000 |
| Mgt Costs (2.52%) | $395,576 |
| **Total:** | $715,576 |

## WHY IS THERE A NEED FOR PARKINSON'S RESEARCH?

**~1 million** people in the U.S. are living with Parkinson's disease[1]

**Certain operational environments and stressors can lead to increased risk for Parkinson's disease[2]**

On average, military deployment yields a **1.8-fold increased** risk to developing Parkinson's disease[3]

Over a 10 year period[4] within the MHS, Parkinson's disease medical encounters for Service Members and beneficiaries included:

- **107,521 patients**
- **2.46 million outpatient encounters**
- **1.81 million hospital bed days**

- The cause of disease **remains largely unknown**; however, scientists believe both genetic and environmental factors contribute[5]
- Globally, Parkinson's disease is the **most common** neurodegenerative movement disorder[6]

## HOW IS THE PROGRAM ADVANCING PARKINSON'S RESEARCH?

In FY22, the PRP specified the following program priorities (left) and directed investments into four types of research (right) to address them.

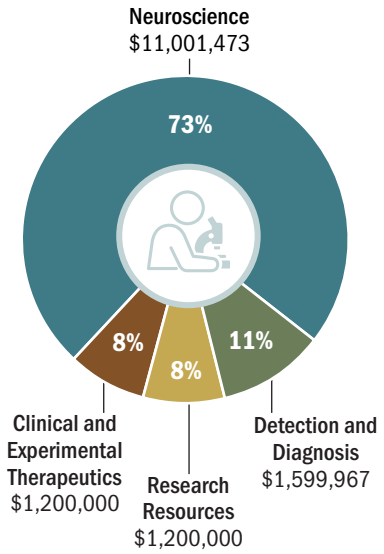
**Biological mechanisms or biomarkers of non-motor symptoms that could lead to...**

**Development of treatments for:**

- Cognitive dysfunction
- Psychiatric dysfunction
- Sleep and circadian rhythms disruptions
- Autonomic dysfunction
- Sensory dysfunction
- Fatigue

**Non-pharmacological interventions, such as:**

- Exercise
- Diet
- Neuro-stimulation therapy
- Neurosurgical




[1] Parkinson's Foundation. 2023. Who has Parkinson's? Miami, Florida. | [2] Military Health System data from the Defense Medical Surveillance System. 2020. The Armed Forces Health Surveillance Division, Defense Health Agency, Silver Spring, Maryland, 2010-2019. | [3] Lorene Nelson, Stanford University School of Medicine, Stanford, CA. "Military service and Parkinson's disease" (W81XWH1110258). | [4] Based on a retrospective study conducted in 2020 with data from 2009-2018. | [5] Parkinson's Foundation. 2023. Causes. Miami, Florida. | [6] World Health Organization. (2023, August 9). Parkinson disease. World Health Organization.

**PROGRAM MISSION:** *To support high-impact Parkinson's research that alters disease progression, improves disease symptoms, and develops treatments that benefit Service Members, Veterans, and all others living with Parkinson's disease*

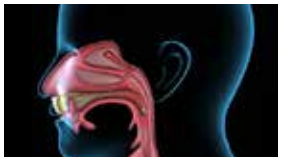
## HOW IS THE PROGRAM MAKING AN IMPACT?


***A Mind in Motion: Exercise Improves Cognitive Flexibility, Impulsivity and Alters Dopamine Receptor Gene Expression***

*Giselle Petzinger, M.D., (left)*
*Daniel Holschneider, M.D., (right)*
*University of Southern California*

**Accomplishment:** With no current effective treatments for cognitive impairment in Parkinson's, Drs. Petzinger and Holschneider collaborated with Dr. Michael Jakowec, University of Southern California, to study physical exercise and its relationship with **improving motor performance** in the disease.

**Impact:** Recent results of this study support that the benefits of exercise include **improved motor function** and **cognitive impairment** for people living with Parkinson's disease.[7]

***Role of Lipid Accumulation in Cognitive Decline***

*D. J. Vidyadhara, Ph.D., Yale University*

**Accomplishments:** Genetic changes in the GBA gene are the biggest risk for severe Parkinson's disease with cognitive problems. In mouse models with genetic changes in GBA, the team found that glycosphingolipids buildup in their brains, which promoted Parkinson's-related protein clumping. They also found a crucial pathway in brain cells responsible for releasing chemical signals related to cognition, called presynaptic endocytosis, was affected due to the glycosphingolipid buildup. Additionally, the team published that issues with presynaptic endocytosis might also be linked to the loss of smell.[8]

**Impact:** Findings will form the basis of **new treatment and preventive strategies** for reducing cognitive decline and loss of smell in people with the disease.



***Understanding the Role of Gene-Environment Interactions in the Degeneration of Human Dopaminergic Neurons***

*Vikram Khurana, M.D., Ph.D., (left) Brigham and Women's Hospital and Harvard Medical School*
*Lee Rubin, Ph.D., (center) Harvard University*
*Beate Ritz, M.D., Ph.D., (right) University of California, Los Angeles*

**Accomplishment:** Seeking to expand on studies that correlate Parkinson's disease with exposure to pesticides, the team investigated **288** pesticides and determined that long-term exposure to **53** of them were associated with the disease.[9] Further analyses revealed that **10** of those pesticides directly affected neurons. The team also analyzed pesticide combinations widely used in cotton farming and found that co-exposures resulted in higher levels of toxicity than any one pesticide by itself.

**Impact:** The outcomes of this comprehensive **field-to-bench paradigm study** of how pesticide exposure increases the risk of Parkinson's disease due to its toxic effect on neurons have the potential to guide the development of future agricultural policy.

"As a consumer member for several years, I've had the opportunity to witness first-hand how the PRP is able to reach out and focus on areas of research need and/or interest that aren't covered by other funding sources, which gives me hope for a breakthrough and help for today in knowing that some of the best researchers/scientists/physicians are able to seek PRP funding."

***Israel Robledo, Michael J. Fox Foundation, Programmatic Panel Member FY16-FY23***

[7] Zhuo W, Lundquist AJ, Donahue EK, et al. 2022. A mind in motion: Exercise improves cognitive flexibility, impulsivity and alters dopamine receptor gene expression in a Parkinsonian rat model. *Current Research in Neurobiology* 100039 (3); DOI: https://doi.org/10.1016/j.crneur.2022.100039. | [8] Martin-Lopez E, Vidyadhara D J, et al. 2023. α-Synuclein Pathology and Reduced Neurogenesis in the Olfactory System Affect Olfaction in a Mouse Model of Parkinson's Disease. *Journal of Neuroscience* 43(6), 1051-1071. | [9] Paul KC, Krolewski RC, Lucumi Moreno, E, et al. 2023. A pesticide and iPSC dopaminergic neuron screen identifies and classifies Parkinson-relevant pesticides. *Nature Communications* 14:2803. https://doi.org/10.1038/s41467-023-38215-z.

# PEER REVIEWED ALZHEIMER'S RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY11, the Peer-Reviewed Alzheimer's Research Program (PRARP) supports broad research focusing on the relationship between traumatic brain injury and Alzheimer's disease.

| *FY22 Congressional Appropriations* |
|---|
| **$15M** |
| *FY22 Research Investment* |
| Accelerating Diagnostics Research Award ..... $4,997,169 |
| Investigator - Initiated Research Award ..... $8,156,887 |
| **Total:** $13,154,056 |
| *FY22 Withholds and Management Costs* |
| USAMRDC ..... $280,142 |
| SBIR/STTR ..... $501,000 |
| Mgt Costs (7.49%) ..... $1,064,802 |
| **Total:** $1,845,944 |

[1] Alzheimer's Association. 2022. Alzheimer's Disease Facts and Figures. https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. | [2] Gardner RC, Bahorik A, et al. 2022. Systematic Review, Meta-Analysis, and Population Attributable Risk of Dementia Associated with Traumatic Brain Injury in Civilians and Veterans. *Journal of Neurotrauma* 40(7-8):620-634. https://doi.org/10.1089/neu.2022.0041. | [3] Military Health System. Be a Brain Warrior: Protect. Treat. Optimize. https://www.health.mil/News/In-the-Spotlight/Be-a-Brain-Warrior. | [4] Kornblith E, Bahorik A, et al. 2022. Association of Race and Ethnicity with Incidence of Dementia Among Older Adults. *The Journal of the American Medical Association* 327(15):1488- 1495. https://doi.org/10.1001/jama.2022.3550. | [5] Alzheimer's Disease International. Dementia Statistics. https://www.alzint.org/about/dementia-facts-figures/dementia-statistics.

## WHY IS THERE A NEED FOR ALZHEIMER'S RESEARCH?

**Alzheimer's disease is the 7th leading cause of death in the U.S.[1]**

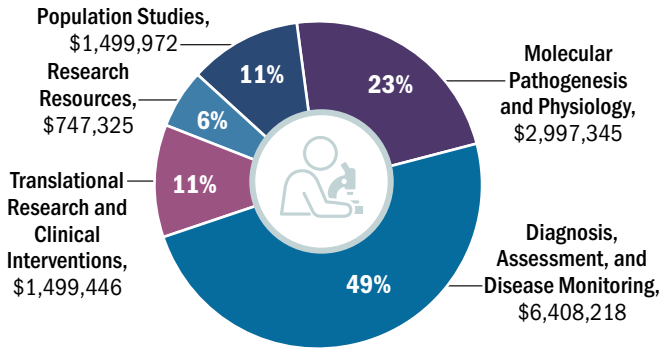
**Service Members with a TBI are 2-8X more likely to develop Alzheimer's disease and related dementias than those without a TBI diagnosis[2]**

**More than 460,000 Service Members received a TBI diagnosis over a 22-year period[3]**

- **1 in 9** Americans, or >6.7 million people, over the age of 65 are living with Alzheimer's disease today, and numbers are expected to increase[1]
- An estimated **110 out of every 100,000** Americans under the age of 45 are diagnosed with early-onset dementia[1]
- Race, gender, and co-morbidities are additional factors that increase risk of Alzheimer's disease and related dementias[4]
- Globally, dementia care costs exceed **$1.3 trillion** per year[5]

## HOW IS THE PROGRAM ADVANCING ALZHEIMER'S RESEARCH?

In FY22, the PRARP invested into five research areas defined by the Common Alzheimer's Disease Research Ontology, a classification system shared across multiple funding organizations.




"I am honored to be a part of the PRARP. As the wife of a Veteran with Alzheimer's disease, I appreciate the need for innovative approaches to study traumatic brain injury in relation to dementia. The impact of studying the relationship between military risk factors and the devastation of brain degeneration as well as possible disease modifiers, caregiver support, and progress toward treatment/prevention will be life-changing. Our Veterans and their Families will greatly benefit from this vital process."

***Sarah Hornback, Alzheimer's Association, Programmatic Panel Consumer Reviewer, FY21-FY23***

**PROGRAM MISSION:** *Support research to (1) understand the association between traumatic brain injury and other military service-related risk factors and Alzheimer's disease/ Alzheimer's disease-related dementias, and (2) improve quality of life and reduce the burden on affected individuals and caregivers for the military, Veterans, and the public.*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Prognosis and Diagnosis**

***Evaluating Effects in the Relationship Between Traumatic Brain Injury and Alzheimer's Disease: Epidemiological Determinants, Their Health-Related Causes, and the Resulting Disparities***

*Igor Akushevich, Ph.D., Duke University*

TBIs are linked to multiple neurodegenerative disorders such as Alzheimer's and Alzheimer's-related dementias in military and civilian populations. However, the causes and mechanisms of this link are yet to be identified. In a recent report, Akushevich conducted an epidemiological study using health records data to determine the relationship between post-TBI cognitive decline and risk factors affecting everyday functioning and quality of life in Veterans and non-Veterans. The team showed **later-life TBI carries an enormously increased risk** in developing Alzheimer's disease and related dementias,[6] and **cardiovascular risk factors, such as hypertension, may play a significant role, particularly among Black Americans**.[7] These insights may lead to improvements in disease prognosis and diagnosis.

**Risk Factors**

***Using Brain Imaging to Predict and Detect Risk Factors for Alzheimer's Disease***

*Andrei Irimia, Ph.D., University of Southern California*

Although there is a known link between Alzheimer's disease and TBI, it is difficult to predict the likelihood that an individual with a TBI will develop Alzheimer's disease. Irimia is **leveraging machine learning to identify risk factors for Alzheimer's disease progression** in aging individuals with cognitive decline by comparing their brain scans and brain activity to those of aging people without cognitive decline. Irimia used this approach to identify differences between chronological age and brain scan-derived brain age to **identify risk factors for cognitive decline post-injury**.[8,9] In addition, by comparing scans of those with normal cognitive aging to those with cognitive decline, the results enable the identification of candidates who could benefit from early intervention to improve their quality of life.

**Digital Aid**

***A Digital Memory Notebook to Support Everyday Functioning, Decrease Caregiver Burden, and Track Health Status***

*Maureen Schmitter-Edgecombe, Ph.D., Washington State University*

Schmitter-Edgecombe and her team developed the Electronic Memory and Management Aid, or EMMA, application that can partner with a smart-home to improve everyday memory and functioning and support positive brain health behaviors in individuals with cognitive impairment. The team identified predictors of long-term adoption of the EMMA app in older adults, including language ability and frequency of app use earlier in training. The team is currently working on novel methods (e.g., automated booster sessions) to **facilitate long-term habit formation and use of digital devices in cognitively impaired adults**. The results indicate smart-home technology and digital apps can be used for individuals experiencing memory decline and potentially applied across multiple interventions.

[6] Yashkin AP, Gorbunova GA, et al. 2023. Differences in Risk of Alzheimer's Disease Following Later-Life Traumatic Brain Injury in Veteran and Civilian Populations. *Journal of Head Trauma Rehabilitation*. https://doi.org/10.1097/HTR.0000000000000865. | [7] Akushevich I, Kolpakov S, et al. 2022. Vulnerability to Hypertension Is a Major Determinant of Racial Disparities in Alzheimer's Disease Risk. *American Journal of Hypertension* 35(8):745-751. https://doi.org/10.1093/ajh/hpac063. | [8] Irimia A, Maher AS, et al. 2020. Acute Cognitive Deficits After Traumatic Brain Injury Predict Alzheimer's Disease-Like Degradation of the Human Default Mode Network. *GeroScience* 42:1411-1429. https://doi.org/10.1007/s11357-020-00245-6. | [9] Yin C, Imms P, et al. 2023. Anatomically Interpretable Deep Learning of Brain Age Captures Domain-Specific Cognitive Impairment. *Proceedings of the National Academy of Science* 120(2):e2214634120. https://doi.org/10.1073/pnas.2214634120. | [10] Schmitter-Edgecombe M, Brown K, et al. 2022. Partnering a Compensatory Application with Activity-Aware Prompting to Improve Use in Individuals with Amnestic Mild Cognitive Impairment: A Randomized Controlled Pilot Clinical Trial. *Journal of Alzheimer's Disease* 85(1):73-90. https://doi.org/10.3233/JAD-215022. | [11] Luna C, Cook DJ, Schmitter-Edgecombe M. 2023. But Will They Use It? Predictors of Adoption of an Electronic Memory Aid in Individuals with Amnestic Mild Cognitive Impairment. *Neuropsychology*. https://doi.org/10.1037/neu0000898.

# PEER REVIEWED CANCER RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in 2009, the Peer Reviewed Cancer Research Program (PRCRP) funds innovative and impactful science for the benefit of Service Members, their Families, Veterans, and the American public within congressionally directed cancer-related topic areas that change annually.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$130M** | |
| *FY22 Research Investment* | |
| Behavioral Health Science Award | $8,629,700 |
| Career Development Award - Fellow Option | $5,326,529 |
| Career Development Award - Scholar Option | $8,947,307 |
| Convergent Science Cancer Consortium Development Award | $6,295,264 |
| Idea Award | $16,850,430 |
| Impact Award | $29,626,667 |
| Translational Team Science Award | $38,525,497 |
| Modification to ongoing awards | $663,262 |
| **Total:** | $114,864,656 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $2,511,183 |
| SBIR/STTR | $4,336,000 |
| Mgt Costs (6.73%) | $8,288,161 |
| **Total:** | $15,135,344 |

## WHY IS THERE A NEED FOR RESEARCH IN 20 DIFFERENT TYPES OF CANCER?

**Operational factors or exposures, such as Agent Orange and other herbicides, ionizing radiation, infectious agents, electromagnetic fields, and TBIs, may lead to an increased risk of cancer for the military population[1]**

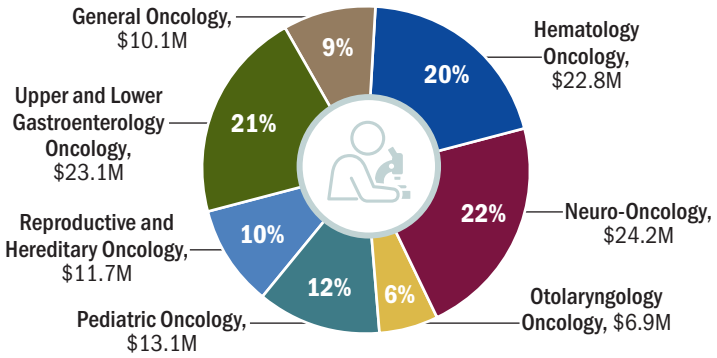
**>50% of cancer-related medical encounters by Service Members in 2022 correlated to a PRCRP topic area[2]**

**Cancer diagnoses in Family members may require Service Members to take time away from duties to provide care for their beneficiaries**

- Through research of multiple cancer types under one program, there is opportunity to **enhance knowledge sharing** across cancer-specific fields for the **benefit of patient communities**
- Investment in research spanning from basic science to clinical studies **addresses the unique needs of each cancer type**

## HOW IS THE PROGRAM ADVANCING CANCER RESEARCH?

The PRCRP directed FY22 program investments into seven cancer portfolios.



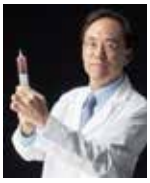

"The PRCRP cancer application review process is quite unique in that it benefits active and Veteran military personnel and their families with a cancer diagnosis. This program is also open to the most brilliant research minds from all around the world. This project is very near and dear to me as a Veteran, and a cancer survivor and advocate"

***Robert Mesloh, Lymphoma Research Foundation, Consumer Reviewer, Programmatic Panel Member, FY19-FY23***

[1] U.S. Department of Veterans Affairs, V. H. A. 2013. Va.gov: Veterans Affairs. Protect your health. https://www.publichealth.va.gov/exposures/. | [2] Armed Forces Health Surveillance Division. 2023. Absolute and Relative Morbidity Burdens Attibutable to Various Illnesses and Injuries Among Active Component Members, U.S. Armed Forces, 2022. *Medical Surveillance Monthly Report* 30(6):7-10.

**PROGRAM MISSION:** *To successfully promote high-impact research for cancer prevention, detection, treatment, quality of life, and survivorship for Service Members, their Families, Veterans, and the American public*

## HOW IS THE PROGRAM MAKING AN IMPACT?



### *Novel Therapy Targets B-Cell Lymphomas*

*Larry Kwak, M.D., Ph.D., City of Hope*

CAR T-cell immunotherapy is a treatment for non-Hodgkin's lymphoma, a cancer affecting white blood cells, including B cells. The therapy works by targeting the cancer through recognition of cell surface proteins, in this case CD19. While effective, some individuals receiving this treatment experience disease recurrence and treatment resistance. To circumvent this issue, Dr. Kwak and his team developed a new CAR T-cell targeting an alternative protein called B-cell activating factor receptor. Through a series of optimization experiments, the team successfully engineered their CAR T-cell to **effectively destroy lymphoma cells** and outperformed the current treatment. This work led to **FDA approval of the new B-cell activating factor receptor CAR T-cell** and laid the groundwork for a phase 1 clinical trial underway through other funding sources.

### *Novel Targets for the Treatment of Metastatic Colorectal Cancer*

*Daniel V. LaBarbera, Ph.D., University of Colorado Anschutz Medical Campus*

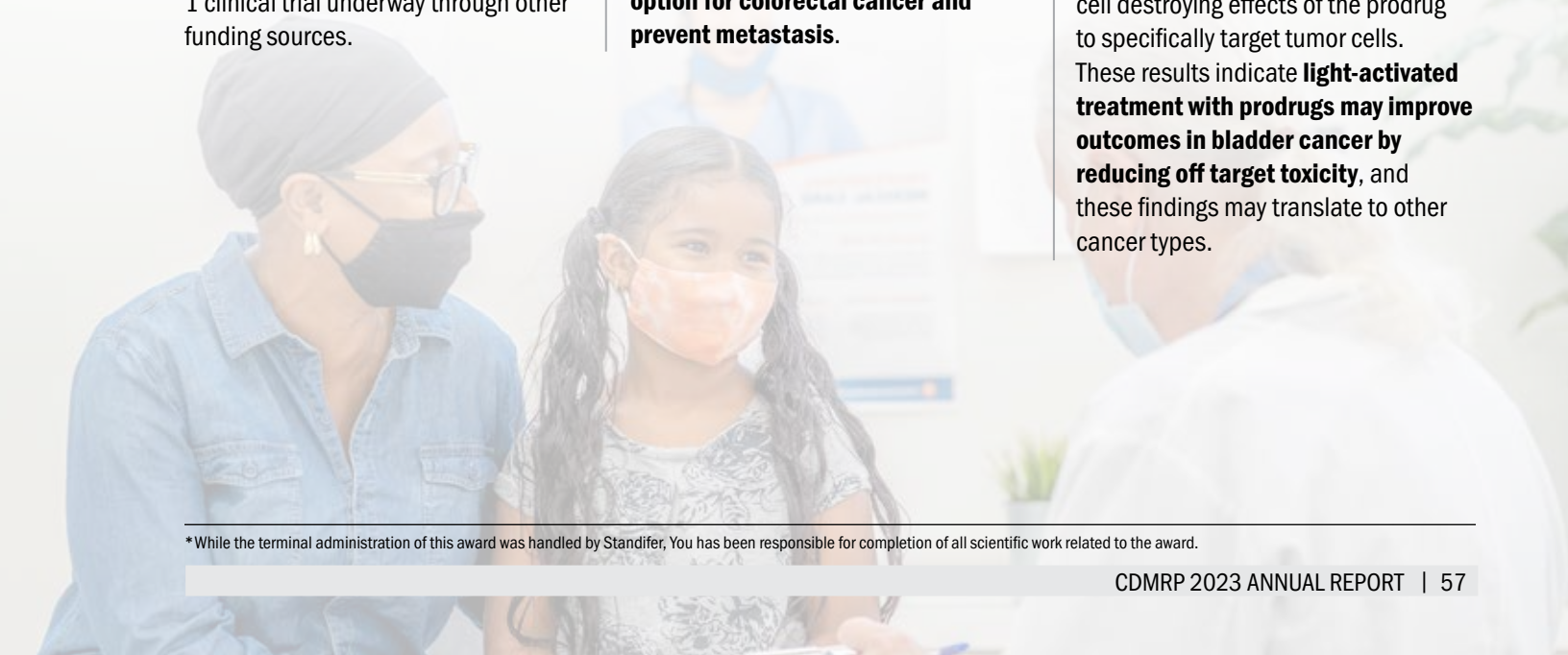
Epithelial-mesenchymal transition is a behavioral change in cancer cells contributing to the development of metastatic colorectal cancer. Through their research, LaBarbera and his team revealed one way to modulate this change is to inhibit a regulatory protein, called TOP2A. The team tested inhibition of TOP2A in combination with a panel of FDA-approved drugs. While conducting these experiments, the team found a second protein, CHDL1, also regulates the epithelial-mesenchymal transition. As a result, they worked to identify an inhibitor to target this second protein. **When combined with current chemotherapies, inhibition of both proteins could lead to a more effective treatment option for colorectal cancer and prevent metastasis**.

### *Therapy Combines Drugs with Photodynamic Therapy*

*Youngjae You, Ph.D., The State University of New York, University at Buffalo**

*Kelly Standifer, Ph.D., University of Oklahoma Health Science Center*

Protoporphyrin IX photodynamic therapy is an approved cancer treatment using a light-activated compound to preferentially target the mitochondria of cancer cells. The research team leveraged this technology to develop **a light-based treatment for early-stage bladder cancer**. Their strategy utilizes prodrugs, which, when triggered by light, are stimulated to the active form by a compound with high concentration in the mitochondria. In a cell and animal model of bladder cancer, the team found coupling the prodrug with light therapy enabled the cell destroying effects of the prodrug to specifically target tumor cells. These results indicate **light-activated treatment with prodrugs may improve outcomes in bladder cancer by reducing off target toxicity**, and these findings may translate to other cancer types.



*While the terminal administration of this award was handled by Standifer, You has been responsible for completion of all scientific work related to the award.

# FY22 PEER REVIEWED CANCER RESEARCH PROGRAM TOPIC AREAS

## HOW IS THIS PROGRAM DIFFERENT FROM OTHER CDMRP RESEARCH PROGRAMS?

In FY22, Congress identified 20 topic areas for the PRCRP of which 19 received program investments. The PRCRP may not use funds to support research into breast, kidney, lung, ovarian, pancreatic, prostate, rare cancers, or melanoma, which are supported by other CDMRP programs.

| | | | | | |
|---|---|---|---|---|---|
| Bladder Cancer | $7.8M 7% | Blood Cancers | $12.4M 11% | Brain Cancer | $19.3M 17% |
| Colorectal Cancer | $8.4M 7% | Endometrial Cancer | $8.2M 7% | Esophageal Cancer | $5.9M 5% |
| Germ Cell Cancers | $5.7M 5% | Head and Neck Cancer | $6.9M 6% | Liver Cancer | $8.0M 7% |
| Lymphoma | $8.0M 7% | Mesothelioma | $0.7M 1% | Metastatic Cancers | $1.6M 1% |
| Myeloma (returning for FY22) | $2.4M 2% | Neuroblastoma | $0.6M 1% | Pediatric, Adolescent, and Young Adult cancers | $6.4M 6% |
| Pediatric Brain Tumors | $4.8M 4% | Stomach cancer | $0.7M 1% | Sarcoma | $5.4M 5% |
| Thyroid Cancer | $1.3M 1% | | | | |

NEW FOR FY22: Von Hippel-Lindau Syndrome Malignancies (excluding cancers of the kidney and pancreas)

# PEER REVIEWED MEDICAL RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in 1999, the Peer Reviewed Medical Research Program (PRMRP) is directed by the U.S. Congress each year to address a wide range of topic areas.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$370M** | |
| *FY22 Research Investment* | |
| Clincal Trial Award | $40,556,192 |
| Discovery Award | $18,738,001 |
| Expansion Award | $46,372,784 |
| Focused Program Award | $42,682,834 |
| Investigator-Initiated Research Award | $79,119,850 |
| Technology/Therapeutic Development Award | $91,272,893 |
| Modification to ongoing awards | $15,910,344 |
| **Total:** | $334,652,899 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $7,144,806 |
| SBIR/STTR | $12,340,000 |
| Mgt Costs (4.53%) | $15,862,215 |
| **Total:** | $35,347,021 |

"The PRMRP directly addresses the most critical clinical issues impacting Wounded Warriors, Veterans, and other Service-connected patients. The PRMRP also addresses orphan diseases while investigating pathways that also affect Wounded Warriors. As a combat surgeon, critical care and critical care air transport team physician, I have been able to provide better care to my patients because of the lessons learned and research supported via this program."

***Retired U.S. Air Force Col. Debra Malone, Programmatic Panel Member, FY22***

## WHY IS THERE A NEED FOR THE MEDICAL RESEARCH PROGRAM?

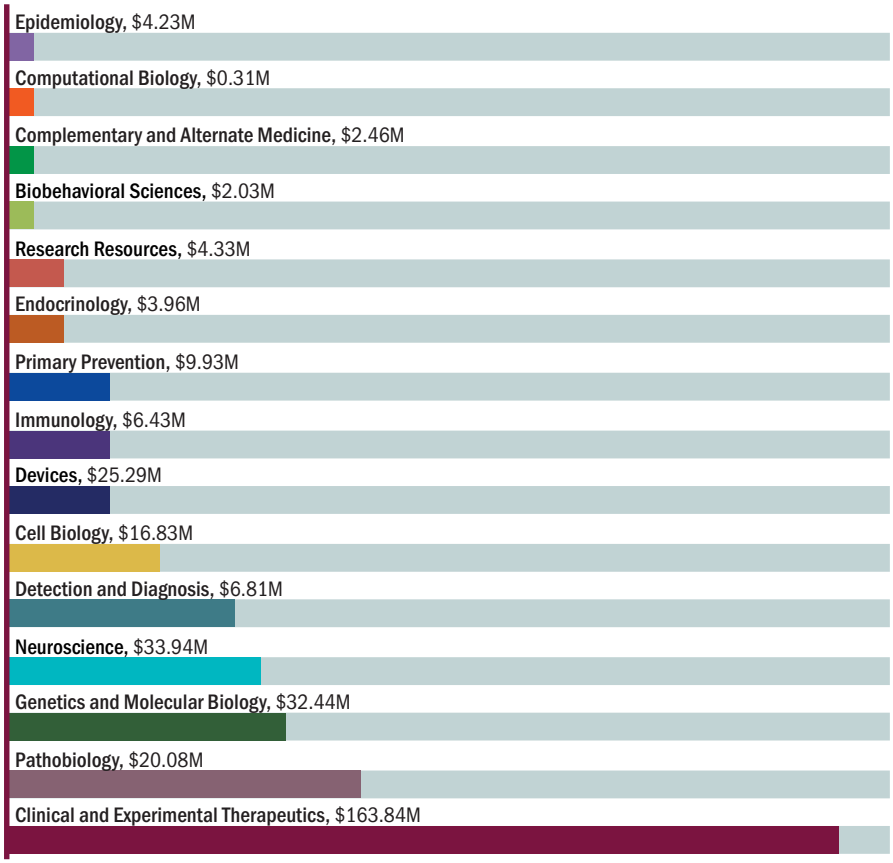
**Funding opportunities for rare and underserved research topics are necessary to address critical healthcare needs for civilians and Service Members**

**>50%**
**of medical encounters by Service Members in 2022 related to PRMRP topic areas[1]**

- **Multiple topics** are addressed under a single program, streamlining administrative costs and maximizing funding for research
- Building a track record of research funding across diverse topics **helps accelerate awareness** and **fosters future investment**

## HOW IS THE PROGRAM ADVANCING MEDICAL RESEARCH?

The PRMRP directed FY22 investments into 15 research types.



**PROGRAM MISSION:** *Encourage, identify, select, and manage medical research projects of clear scientific merit that lead to impactful advances in health care of Service Members, Veterans, and beneficiaries*

## HOW IS THE PROGRAM MAKING AN IMPACT?

### Autoimmune Diseases and Immunology

***Exploiting Inhibitory Cell Surface Molecules to Combat Food Allergies***

*Michael Kulis, Ph.D., University of North Carolina*

Administration of synthetic ligands targeting CD22, a molecule found on the surface of peanut-specific memory immune cells, **increases tolerance to peanut allergens** in a preclinical animal model.

### Cardiovascular Health

***Growth-Adaptive Pediatric Heart Valves to Address a Critical Unmet Need for Infants and Young Children***

*Corin Williams, Ph.D., The Charles Stark Draper Laboratory, Inc.*

The Low-force Expanding/Adaptable Pediatric, also known as LEAP™, valve is undergoing testing under conditions that **mimic "growing" in the heart of a child from infancy to age five**.

### Hemorrhage Control and Blood Products

***Enhancing Transfusable Platelets Using Novel RNA Formulations***

*Christian Kastrup, Ph.D., Versiti Wisconsin, Inc.*

The research team produced preliminary data demonstrating the functional similarity between genetically modified mRNA-lipid nanoparticles and clinically transfused platelets, an **important step toward improving hemorrhage control during prolonged care on the battlefield**.

### Infectious Diseases

***A Phase 2a Study to Evaluate the Cross-Protective Efficacy of M2SR in an Influenza Challenge Model***

*Pamuk Bilsel, Ph.D., FluGen, Inc.*

This completed clinical trial demonstrates intranasal vaccination with M2R2, a strain of influenza, is safe, well-tolerated, and **protects healthy individuals from infection and respiratory illness caused by a variety of flu strains**.

### Internal Medicine

***Evaluation of Pirfenidone for Acute Pancreatitis***

*Vikas Dudeja, M.B.B.S., University of Alabama at Birmingham*

The team successfully received approval from the FDA on their Investigational New Drug application for pirfenidone as a **therapy in patients with predicted moderate to severe acute pancreatitis**, which will allow for a pilot clinical trial to proceed.

### Neuroscience

***Cryoanalgesia to Treat Postamputation Phantom Limb Pain***

*Brian Ilfeld, M.D., University of California, San Diego*

This completed clinical trial demonstrates below-the-knee amputees given cyroneurolysis, the application of cold temperatures to nerves for therapeutic purposes, experienced decreased pain intensity up to four months postamputation, **providing prolonged relief from phantom limb pain**.

### Nutrition and Metabolism

***Novel Mechanism-of-Action Therapeutics to Combat Type 2 Diabetes in U.S. Veterans***

*Harshini Neelakantan, Ph.D., Ridgeline Therapeutics, LLC*

The research team received a patent for their lead compound, RLT-72848, which completed **preclinical safety and toxicology studies to allow for a future clinical trial**.

### Orthopaedic Medicine

***Prevention of Posttraumatic Osteoarthritis with CD9 Inhibitors***

*Dominik Haudenschild, Ph.D., University of California, Davis*

The study team demonstrates microparticles containing flavopiridol, an inhibitor of the CD9 kinase, as a **promising biomaterial platform for sustained small molecule drug delivery** to the joint space and as a potential therapeutic for posttraumatic osteoarthritis.

### Respiratory Health

***Development of DF-COV for the Treatment and Prevention of COVID-19 and Associated Respiratory Complications***

*Gordon Freeman, Ph.D., Dana-Farber Cancer Institute*

The study team demonstrated DF-COV, a compound that **targets proteins on the surface of the SARS-CoV-2 virus**, is capable of neutralizing the virus and is poised to undergo further development for use in clinical trials.

[1] Armed Forces Health Surveillance Division. 2023. Absolute and Relative Morbidity Burdens Attributable to Various Illnesses and Injuries Among Active Component Members, U.S. Armed Forces, 2022. *Medical Surveillance Monthly Report* 30(6):7-10.

# FY22 PEER REVIEWED MEDICAL RESEARCH PROGRAM TOPIC AREAS

## HOW IS THIS PROGRAM DIFFERENT FROM OTHER CDMRP RESEARCH PROGRAMS?

In FY22, Congress identified 50 topic areas for the PRMRP, including six new and four returning topic areas. The PRMRP directed FY22 investments into nine portfolios encompassing the congressionally directed topic areas.

### Autoimmune Disorders and Immunology — $9.73M — 6%

- Food Allergies, $0.32M
- Guillain-Barre Syndrome*
- Inflammatory Bowel Diseases, $8.77M
- Rheumatoid Arthritis, $0.64M

### Cardiovascular Health — $39.99M — 11%

- Cardiomyopathy, $23.86M
- Congenital heart disease, $2.76M
- Familial Hypercholesterolemia
- Hypercholesterolemia, $0.29M
- Hypertension, $3.99M
- Vascular Malformations, $7.29M
- Women's Heart Disease, $1.80M

### Hemorrhage Control and Blood Products — $5.20M — 2%

- Hemorrhage Control
- Pathogen-Inactivated Blood Products, $0.22M
- Platelet-Like Cell Production
- Trauma, $23.24M

### Infectious Diseases — $34.77M — 8%

- Hepatitis B, $0.30M
- Malaria, $5.19M
- Plant-Based Vaccine, $18.05M
- Viral Diseases, $11.24M

### Internal Medicine — $48.80M — 16%

- Ehlers-Danlos Syndrome, $0.31M
- Endometriosis, $0.96M
- Epidermolysis Bullosa, $9.22M
- Focal Segmental Glomerulosclerosis, $11.57M
- Interstitial Cystitis*
- Nephrotic Syndrome
- Pancreatitis, $14.77M*
- Polycystic Kidney Disease, $12.13M
- Pressure Ulcers, $9.36M

### Neuroscience — $53.01M — 15%

- Dystonia, $4.18M
- Eating Disorders, $7.40M
- Fragile X, $0.31M
- Friedreich's Ataxia, $9.16M
- Frontotemporal Degeneration, $7.68M
- Hydrocephalus, $19.20M
- Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome
- Myotonic Dystrophy, $8.85M
- Non-Opioid Therapy for Pain Management, $13.57M
- Peripheral Neuropathy, $4.64M
- Rett Syndrome, $0.66M*
- Sleep Disorders and Restriction, $13.10M
- Suicide Prevention, $5.86M

### Nutrition and Metabolism — $14.18M — 6%

- Diabetes, $6.77M
- Mitochondrial Disease, $0.93M
- Nutrition Optimization, $3.64M

### Orthopaedic Medicine — $33.40M — 8%

- Arthritis, $11.29M
- Fibrous Dysplasia, $3.35M
- Musculoskeletal Disorders (related to acute and chronic bone conditions and injuries), $14.63M

### Respiratory Health — $29.97M — 10%

- Pulmonary Fibrosis, $5.05M
- Respiratory Health, $14.49M

### Spans Across Portfolios

- Sustained Release Drug Delivery, $11.88M
- Trauma, $23.24M

New in FY22

*Returning Topic Areas were identified by Congress in or before FY20 and identified again in FY22.

# PEER REVIEWED ORTHOPAEDIC RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in 2009, the Peer Reviewed Orthopaedic Research Program (PRORP) aims to support orthopaedic and other trauma research, treatment and rehabilitation including regenerative medicine, for optimal recovery from traumatic injuries.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$30M** | |
| *FY22 Research Investment* | |
| Applied Research Award | $6,524,057 |
| Clinical Translational Research Award | $10,953,564 |
| Clinical Trial Award | $9,211,137 |
| Modification to ongoing awards | $469,403 |
| **Total:** | $27,158,161 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $579,980 |
| SBIR/STTR | $1,001,000 |
| Mgt Costs (4.44%) | $1,260,859 |
| **Total:** | $2,841,839 |

[1] The United States Bone and Joint Initiative. 2023. Lost Work Days. https://bmus.latticegroup.com/fourth-edition/id2/lost-work-days. | [2] U.S. Army Public Health Center. Health of the Force. 2018. https://phc.amedd.army.mil/Periodical%20Library/2018%20Health%20of%20the%20Force%20report%20-%20web.pdf. | [3] Mitchell SL, Hayda R, et al. 2019. METALS Study Group. The Military Extremity Trauma Amputation/Limb Salvage (METALS) Study: Outcomes of Amputation Compared with Limb Salvage Following Major Upper-Extremity Trauma. *Journal of Bone & Joint Surgery* 101(16):1470-1478. | [4] Molloy JM, Pendergrass TL, et al. 2020. Musculoskeletal Injuries and United States Army Readiness Part I: Overview of Injuries and their Strategic Impact. *Military Medicine* 185(9-10):e1461-e1471.

## WHY IS THERE A NEED FOR ORTHOPAEDIC RESEARCH?

**>35 million** adults with a musculoskeletal injury reported lost work days in a single year, totaling nearly 364 million days[1]

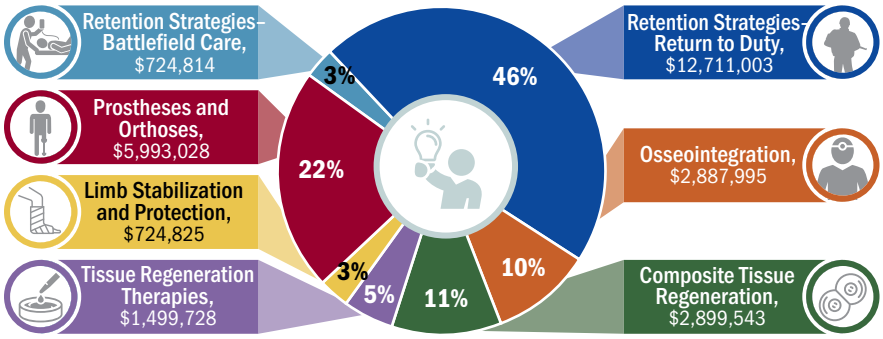
Musculoskeletal injuries affect **>50%** of Soldiers and are responsible for 10 million limited-duty days annually[2]

More than **70%** of active-duty injuries are due to cumulative micro-traumatic musculoskeletal "overuse" injuries[2]

- **52%** of military combat wounds include extremity injury, and battlefield orthopaedic injuries are a major cause of long-term disabilities[3]
- Non-combat injuries and conditions present a major threat to military personnel readiness and result in **2 million** outpatient medical encounters a year[4]

## HOW IS THE PROGRAM ADVANCING ORTHOPAEDIC RESEARCH?

In FY22, the PRORP directed investments into seven program priority areas.




No applications to Compartment Syndrome and/or Reperfusion Injury and Translation of Early Findings were funded in FY22

"[Researchers] don't directly benefit from their work as they typically do not have the injuries or conditions that they intend to treat, yet they throw themselves at their work. It's truly selfless, and I thank them."

***Retired U.S. Navy Petty Officer 2nd Class Tyler Burdick, Semper Fi Fund, Peer Reviewer, FY18-21***

**PROGRAM MISSION:** *Address the most significant gaps in care for the leading burden of injury and for facilitating return to duty by funding innovative, high-impact, clinically relevant research to advance optimal treatment and rehabilitation from musculoskeletal injuries sustained during combat and service-related activities*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Prostheses and Orthoses**

***Improved Daily Comfort and Mobility for Lower-Limb Amputees Using Novel Release-Relock System***

*Joan Sanders, Ph.D., University of Washington*

Sanders and her team developed and tested the To Auto-release & Relock a PIN, or TARPIN system, a novel technology using a motor-driven tether to **permit quick and easy socket release**, partial removal during sitting, and subsequent relock prior to standing. Such ease allows individuals with lower limb amputation to discreetly relieve pressure placed on their residual limb caused by the prosthetic socket.

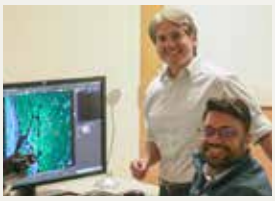
**Retention Strategies-Return to Duty**

***Cognitive Function and ACL Rehabilitation***

*Dustin R. Grooms, Ph.D., AT, CSCS, Ohio University*

Grooms and his team quantified brain activity in high-risk and ACL injury-repaired individuals to help identify the regions affected and develop **new rehabilitation strategies** to best address their needs. This work also demonstrated the benefits of incorporating environment and cognitive load in **training tools for increased performance and injury prevention** and shows the importance of cognitive function in physical rehabilitation.

**Tissue Regeneration Therapies**



***Pre-Innervated Muscle Complexes: A New Avenue for Treatment of Volumetric Muscle Loss***

*D. Kacy Cullen, Ph.D., and Suradip Das, Ph.D., Corporal Michael J. Crescenz Veterans Affairs Medical Center*

Cullen and Das developed a tissue-engineered product that incorporates nerves into the product to help regenerate the surrounding muscle. The researchers recently demonstrated their **tissue-engineered product leads to increased muscle growth and functional recovery** in a clinically relevant volumetric muscle loss animal model.

**Prostheses and Orthoses**

***Clinician-Friendly Algorithm to Create Low-Cost, Customizable Prosthetic Feet: Biomechanical Evaluation of User-Specific Prosthetic Feet Using the Lower Leg Trajectory Error Framework***

*Amos Winter, Ph.D., Massachusetts Institute of Technology*

Winter and his team created an algorithm that customizes biometric information that clinicians can use to create low-cost, plastic prosthetic feet personalized to patients' body weight and size to induce desired walking biomechanics. Their findings suggest a potential avenue to **improving amputees' quality of life** by providing **personalized, plastic prosthetic feet** that can be manufactured and sourced at much lower costs than existing products.

**Retention Strategies-Return to Duty**

***New Information on Our Understanding of Osteoarthritic Onset***

*Tamara Alliston, Ph.D., University of California, San Francisco*

Alliston and her team researched communication between osteocytes, or mature bone cells, during osteoarthritis and the role of certain enzymes in maintaining osteocyte communication and function. The team discovered a reduced number of these enzymes in patient tissues and that mouse models exhibited osteoarthritis disease symptoms when the gene responsible for creating those enzymes was inhibited. The result of Alliston's work **advances the understanding of osteoarthritis mechanisms associated with disease development and could significantly impact advancing osteoarthritis treatment for those suffering from chronic joint disease**.

# PROSTATE CANCER RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Since FY97, the Prostate Cancer Research Program (PCRP) has supported multi-institutional, multi-disciplinary, and clinically focused research placing special emphasis on disparities-driven differences in the diagnosis and treatment of prostate cancer.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$110M** | |
| *FY22 Research Investment* | |
| Data Science Award | $4,999,561 |
| Early Investigator Research Award | $7,339,189 |
| Exploration-Hypothesis Development Award | $3,017,839 |
| Health Disparity Research Award | $9,351,123 |
| Idea Development Award | $48,248,771 |
| Physicians Research Award | $7,602,571 |
| Translational Science Award | $10,938,658 |
| Modification to ongoing awards | $7,768,215 |
| **Total:** | $99,265,927 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $2,098,624 |
| SBIR/STTR | $3,672,000 |
| Mgt Costs (4.76%) | $4,963,449 |
| **Total:** | $10,734,073 |

## WHY IS THERE A NEED FOR PROSTATE CANCER RESEARCH?

**Estimated 288,300 new diagnoses and 34,700 deaths from prostate cancer in the U.S. in 2023**[1]

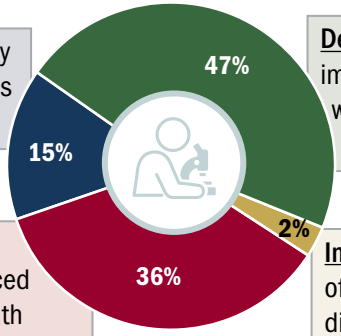
**211,625 Active Service Members and DOD beneficiaries were treated for prostate cancer in the MHS over a 10 year period**[2]

**~80% of the active-duty population are men**[3]

- Current treatments can result in urinary, bowel, and sexual dysfunction.[4]
- The American Cancer Society suggests that African American men are **1.73X** higher incidence, and **2.13X** higher mortality.[5]

## HOW IS THE PROGRAM ADVANCING PROSTATE CANCER RESEARCH?

In FY22, the PCRP directed investments into four program priority areas.




**Advance** health equity and reduce disparities $13,568,300

**Develop** treatments that improve outcomes for men with advanced disease $43,748,143

**Define** the biology of progression to advanced disease to reduce death $33,560,355

**Improve** quality of life for all of those impacted by the disease, $1,849,436

"I've been involved as a consumer reviewer with the PCRP since 2019 and I truly feel that my input as a survivor makes a huge difference. I'm truly amazed at the level of effort the research community commits to improving prostate cancer treatment and the quality of life of those impacted. These efforts address important issues in the patient community, lack of knowledge/information, and fear of side effects/quality of life. My father, my oldest brother, and I all served in the U.S. Army. The PCRP is clear evidence of the government's involvement and support for U.S. Veterans and all patients impacted by this disease."

***Dwight Moore, Arkansas Prostate Cancer Foundation, Consumer Peer Reviewer FY19-FY22, Programmatic Panel Member FY23***

[1] American Cancer Society. 2023. Cancer facts and figures 2023. Atlanta, GA. | [2] Military Health System (MHS) data from the Defense Medical Surveillance System, 2010-2019. The Armed Forces Health Surveillance Division, Defense Health Agency (DHA), Silver Spring, MD, November 2020. | [3] Department of Defense (n.d.). Department of Defense Releases Annual Demographics Report – Upward Trend in Number of Women Serving Continues. https://www.defense.gov/News/Releases/Release/Article/3246268/department-of-defense-releases-annual-demographics-report-upward-trend-in-numbe/. | [4] American Society of Clinical Oncology. 2023. Prostate Cancer: Types of Treatment 2022. Alexandria, VA. December 14, 2022. | [5] https://doi.org/10.3322/caac.21718.

**PROGRAM MISSION:** *Fund research that will eliminate death and suffering from prostate cancer and enhance the well-being of Service Members, Veterans, and all the men and their Families who are experiencing the impact of the disease*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**DNA Vaccines**

***Treatment of Prostate Cancer Using Targeted Radionuclide Therapy with Tumor-Specific T-Cell Activation***

*Douglas McNeel, Ph.D., University of Wisconsin-Madison*

McNeel's team found that depletion of regulatory T-cells combined with immunotherapy and **targeted radionuclide therapy** led to a substantial antitumor response. Vaccination with high-dose targeted radionuclide therapy, plus a particular DNA vaccine, increased tumor-infiltrating cells, called memory CD8 T cells. McNeel is continuing his research with an existing award in order to explore clinical applications that may improve the efficacy of immunotherapy.[6]

**Disease Modeling**

***Addressing Treatment Resistance in Models of Lethal Prostate Cancer by Identifying Novel Targets for Drug Discovery***

*Alessandro Vasciaveo, Ph.D., Columbia University Medical Center*

Vasciaveo's team developed a computational precision oncology framework, **OncoLoop**, that supports rapid-turnaround co-clinical studies to identify and validate drugs for individual patients, which can then be **readily adapted for clinical practice**. Applied to lethal prostate cancer patient data, OncoLoop predicted drugs that enhanced the efficacy of clinically relevant therapies including nivolumab and enzalutamide.

**African American Patients**

***Frequent Loss of CHD1 in the Prostate Cancer of African Americans and Its Potential Role in Increased Sensitivity to Platinum or PARP Inhibitor-Based Therapy***

*Zoltan Szallasi, M.D., Ph.D., Children's Hospital, Boston*

Dr. Szallasi's team found that **deletion of the gene CHD1 is three times as frequent in the prostate cancers of African American men** relative to European American men, and leads to increased sensitivity to talazoparib. A clinical protocol to identify loss of CHD1 in African American patients will likely lead to more effective therapeutic use of talazoparib and a reduction in disparity-driven mortality.

**Drug Resistant Cancer**

***Investigating the Genomic Evolution of Metastatic Castration-Resistant Prostate Cancer (mCRPC)***

*Felix Feng, M.D., Ph.D., University of California, San Francisco*

An estimated **15%-20%** of **mCRPC patients** with resistance to abiraterone and enzalutamide have genetic mutations that trigger the expression of the androgen receptor, which promotes drug resistance. Dr. Feng's team compared the genomes of mCRPC patients before and after developing androgen receptor therapy resistance to reveal novel mechanisms of therapeutic resistance.

**Team Science**

***The Prostate Cancer Clinical Trials Consortium (PCCTC): Application for Coordinating Center with Affiliate Clinical Research Sites***

*Howard Scher, M.D., Sloan Kettering Institute for Cancer Research*

The PCRP-funded PCCTC launched a collaborative effort to create a **patient registry** called IRONMAN, International Registry for Men with Advanced Prostate Cancer. The consortium leveraged PCRP funding, plus support from industry partners, to collect data from **5,000** patients in **15** countries to improve survival, understand patient-reported outcomes, and enhance understanding of treatment resistance. A report describing this effort and its outcome to date was recently published in the *Journal of Global Oncology*.[7]

[6] Gamat-Huber M, Jeon D, et al. 2020. Treatment combinations with DNA vaccines for the treatment of metastatic castration-resistant prostate cancer (mCRPC). *Cancers* 12:2831. | [7] Mucci LA, Vinson, J, Gold T, et al. 2022. IRONMAN: A novel international registry of men with advanced prostate cancer. *JCO Global Oncology* 8. e2200154. Published online November 4, 2022. https://doi.org/10.1200/GO.22.00154.

# RARE CANCERS RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in 2020, the Rare Cancers Research Program (RCRP) supports research that greatly improves outcomes for people with rare cancers through discovery, community building, and expansion of knowledge across the cancer landscape.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$17.5M** | |
| *FY22 Research Investment* | |
| Concept Award | $1,956,295 |
| Idea Development Award | $11,712,955 |
| Resource Community Development Award | $1,841,622 |
| **Total:** | $15,510,872 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $295,723 |
| SBIR/STTR | $584,000 |
| Mgt Costs (6.68%) | $1,109,405 |
| **Total:** | $1,989,128 |

"Every person in the room during the programmatic review meetings approached each discussion with confidence in their area of expertise, as well as humility and an open mind, and always with high regard for the ultimate impact on the patient and caregiver community. I have enormous gratitude for the work being done in the scientific community, and I now have the unique perspective of witnessing the commitment those folks have to benefiting those who rely on their scientific efforts the most."

***Lori Stephen, National Brain Tumor Society, Programmatic Panel Member, FY20-FY22***

## WHY IS THERE A NEED FOR RARE CANCER RESEARCH?

**In the U.S., ~25% of all cancer deaths each year are due to rare cancers[1]**

**Rare cancer patients are ~7X less likely to have an approved targeted therapy[2]**

**~16% of cancers in the VA are rare in nature[3] and there are ~8,000 new cases per year[4,5]**

## HOW IS THE PROGRAM ADVANCING RARE CANCER RESEARCH?

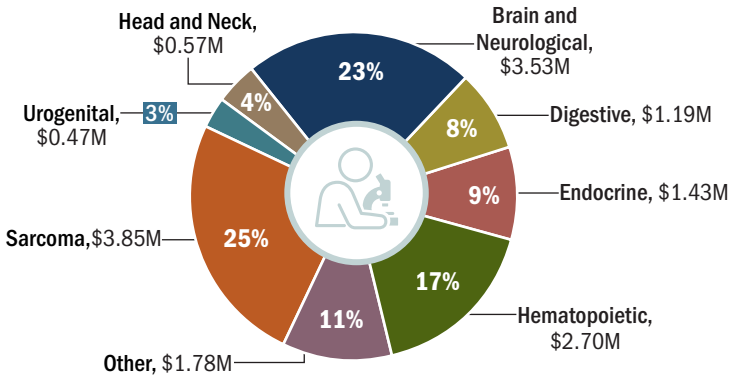
The RCRP established the following program priorities (top) and directed FY22 investments into eight rare cancers (bottom).

**Research Models**
Develop and validate rare tumor-specific models that can support clinical trial readiness

**Biology**
Identifying disease-defining molecular pathways, cell context, and micronenvironment

**Therapy**
Develop therapeutic strategies

**Platform Development**
Sharing data, biospecimens, and resources




[1] DeSantis CE. 2017. The Burden of Rare Cancers in the United States. *A Cancer Journal for Clinicians* 67:261-272. | [2] Rare Cancer's "Valley of Death." 2019. American Association of Cancer Researchers, Abstract 2505. in the U.S. | [3] VA's Progress on Treating Cancer Since 2016. 2022. *VA News*. https://news.va.gov/101361/vas-progress-on-treating-cancer-since-2016/. | [4] Seigel RL, et al. 2018. *A Cancer Journal of Clinicians*. | [5] Zullig LL, Sims KJ, et al. 2017. Cancer Incidence Among Patients of the U.S. Veterans Affairs Health Care System: 2010 Update. *Military Medicine* 182(7):e1883-e1891.

**PROGRAM MISSION:** *Elevate rare cancers research to catalyze knowledge building and enable clinically impactful discoveries for the benefit of Service Members, their Families, Veterans, and/or the American public*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Data Sharing**

*Network for Rare Tumors of the Ovary*

*William Foulkes, Ph.D., McGill University Health Centre Research Institute*

Foulkes oversaw the establishment of the Network for Rare Tumors of the Ovary, an international collaboration of researchers, clinicians, charities, patient advocacy organizations, and experts in data dissemination to **advance knowledge of specific forms of rare ovarian cancers**. The network collects and shares data and biological samples through a web portal accessible to researchers and patients worldwide. The network consists of two data hubs located at Montreal, Canada and Barcelona, Spain. The network already collected existing data and samples from some existing datasets and biobanks and is currently adding new data and samples over time as participants are recruited directly into the network biobanks. Open sharing of the collected data and resources **will improve researchers' ability to study and understanding of these rare ovarian cancers and outcomes for patients**.

**Novel Mouse Model**

*Identifying the Role of the Extracellular Matrix in Rare Cancer Progression*

*Brian Rubin, M.D., Ph.D., Cleveland Clinic Foundation*

Epithelioid hemangioendothelioma, a rare and aggressive cancer that arises from cells that line blood vessels, has no effective treatment options. Dr. Rubin and his team developed a novel genetically engineered mouse model of the disease to test their theory that this cancer is caused by the fusion of two genes, TAZ and CAMTA1. The team also developed an aggressive model of the disease by deletion of a gene, CDKN2A, and subsequently developed cell line and pre-clinical models. Using their newly developed models, they investigated whether trametinib, an FDA-approved drug, blocked the signals from a gene that triggers tumor growth. These novel mouse models and cell lines will help researchers **better understand the cancer's biology and potentially lead to the development of treatment options**.

**Novel Targeted Therapy**

*Targeting an RNA Modification Protein for Use in Cancer Therapy*

*Tao Liu, Ph.D., University of New South Wales*

Neuroblastoma is a type of cancer that develops in young nerve tissue and typically affects children under the age of 5. Survival rates for the high-risk form of this cancer are very low, despite the availability of multiple treatment options. Liu and his team suspected that a particular protein, called RNA methyltransferase, plays a critical role in neuroblastoma tumor progression and sought to define the role played in the proliferation of neuroblastoma cells. The team found inhibiting the protein led to **reduced tumor growth and enhanced survival rates.** These results suggest the **potential for developing a novel targeted therapy that can be developed for clinical use**.

**Novel Immunotherapies**

*Macrophage-Based Immunotherapy for Light Chain Amyloidosis*

*Jing Fu, Ph.D., Columbia University Medical Center*

Light chain amyloidosis, a rare and incurable disease, is caused by abnormal light chains produced by bone marrow plasma cells, which form insoluble fibers and leads to destruction of tissues and organs. Fu and her team modified a special type of white blood cell, called a chimeric antigen receptor macrophage, to attack and break up these abnormal fibers. The team used cell assays to test the efficacy of this approach and found the modified white blood cells successfully cleared amyloidosis fibers. This outcome suggested the feasibility of **developing novel immunotherapies for treating amyloidosis and significantly improving patient outcomes**.

# RECONSTRUCTIVE TRANSPLANT RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in 2012, the Reconstructive Transplant Research Program (RTRP) supports the basic, translational, and clinical research needed to improve access to reconstructive transplants and state-of-the-art immunotherapy.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$12M** | |
| *FY22 Research Investment* | |
| Advanced Technology Development Award | $1,498,893 |
| Clinical Network Award | $3,000,000 |
| Concept Award | $599,595 |
| Investigator-Initiated Research Award | $5,475,130 |
| Qualitative Research Award | $750 |
| **Total:** | $10,574,368 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $232,000 |
| SBIR/STTR | $400,000 |
| Mgt Costs (6.98%) | $793,632 |
| **Total:** | $1,425,632 |

"I'm glad this funding exists to let me be in the position I'm in now to get some of my independence back and have a hand for holding my daughter's."

***Joe Kinan (hand transplant recipient), Programmatic Panel Member, FY21-FY23***

## WHY IS THERE A NEED FOR RECONSTRUCTIVE TRANSPLANT RESEARCH?

**Upper extremity limb loss affects ~41,000 Americans**[1]

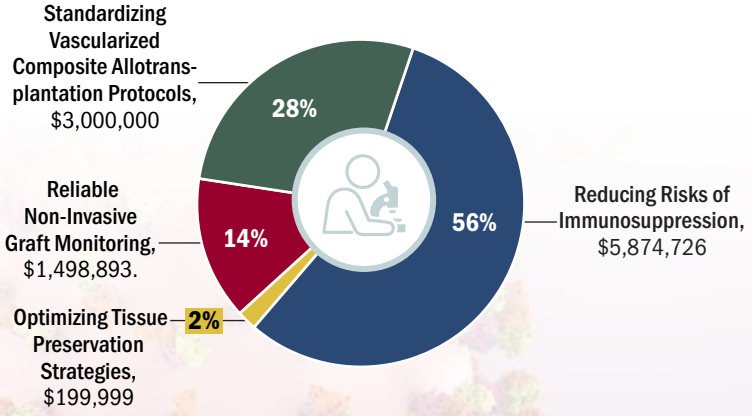
**During 2020 in the U.S., 35,387 head and neck reconstructive procedures occurred**[2]

**1,558 military personnel lost a limb in the Iraq and Afghanistan wars**[3]

## HOW IS THE PROGRAM ADVANCING RECONSTRUCTIVE TRANSPLANT RESEARCH?

The RTRP established seven program priorities (top), addressed by FY22 investments (bottom).

| | | |
|---|---|---|
| **Reducing** risks of immunosuppression | **Optimizing** tissue preservation strategies | **Customizing** functional outcome measures |
| **Restoring** full function | **Reliable** non-invasive graft monitoring | **Understanding** psychosocial factors |
| **Standardizing** vascularized composite allotransplantation protocols | | |




[1] Dillingham, Timothy R. & Braza, Diane W. 2007. Upper Limb Amputations. Essentials of Physical Medicine and Rehabilitation. Second Edition. https://www.sciencedirect.com/topics/nursing-and-health-professions/arm-amputation. | [2] Donor Alliance. Transplant Centers. 2023. https://www.donoralliance.org/professional-partners/transplant-centers/. | [3] Amputee Coalition. 2021. Limb Loss in the U.S. https://acl.gov/sites/default/files/programs/2021-04/llam-infographic-2021.pdf. | [4] https://www.withinreach.info/.

**PROGRAM MISSION:** *Advance science and standardized clinical practice of vascularized composite allotransplantation to improve access, safety, and quality of life for catastrophically injured Service Members, Veterans, and American civilians*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Inflammatory Response**

***Researching New Ways to Block Inflammation and Prevent Severe Tissue Damage Following Transplantation***

*Christene A. Huang, Ph.D., University of Colorado*

Vascularized composite allotransplantation, the transplant of several tissue types at one time, can lead to ischemia reperfusion injury or cell death after reintroduction of the blood supply and subsequent inflammation. Huang's team studied the effect of blocking Galectin-3, a protein involved with inflammatory responses, in an animal transplant model with induced ischemia reperfusion injury. Blockade of the protein significantly reduced inflammatory response to ischemic injury, **indicating this approach could improve outcomes for transplant recipients**.

**Informed Consent**

***Ethical Factors Impacting Decisions to Pursue Vascularized Composite Allotransplantation***

*Elisa Gordon, Ph.D., M.P.H., (top left) Vanderbilt University Medical Center; Scott Tintle, M.D., (top right) Walter Reed National Military Medical Center; Macey Levan, J.D., Ph.D., (bottom left) New York University; and Gerald Brandacher, M.D., (bottom right) Johns Hopkins University*

Candidates for vascularized composite allotransplantation may be inadequately informed of the risks of the procedure due to inconsistent informed consent processes across transplant centers. Gordon and collaborators examined the responses from 169 transplant candidates and their families about the decision-making processes, psychosocial concerns, and information needs. The team developed a question prompt sheet to facilitate conversation and aid decision-making processes for transplant candidates and their care providers.[4] Eighty-six percent of participants indicated a willingness to utilize the tool. This new tool may **help transplant centers establish realistic expectations for candidates and improve patient outcomes**.

**Immune Response**

***Bioengineered Particles to Promote Regulatory T Cells and Modulate the Immune System***

*Giorgio Raimondi, Ph.D., Johns Hopkins University*

Following a transplant, the body naturally responds by rejecting the new tissue, requiring transplant recipients to take medication throughout their lifetime. The medication suppresses the immune response, leaving the patient more vulnerable to infection, cancer, and medication-induced kidney disease. Raimondi and his team developed biodegradable particles selectively targeting T regulatory cells, or Tregs. Tregs are a type of immune cell responsible for suppressing other cells of the immune system to prevent the body from attacking itself. Raimondi's team demonstrated the ability to expand and activate mouse and human Tregs with an engineered fusion protein called an immunocytokine. The fusion protein combines a Treg-stimulating agent, interleukin-2, and an antibody that specifically recognizes and attaches to Tregs, making the agent available to just Tregs and limiting off-target effects. These results lay the groundwork for developing a Treg-targeting **immunotherapy for modulating the immune system to prevent transplant rejection**.

"As a TBI and other injury survivor, I have found that working with the CDMRP community, specifically RTRP, has been very enlightening. Taking part in the peer reviews has allowed me to peek behind the scenes, as it were, to see how and why treatment in these fields happens. It has given me a new respect for the researchers and administrative side of medicine. Being allowed to participate as a layperson "consumer reviewer" has given me one more way I can use my experiences to help other Veterans and injury survivors."

***Kent Phyfe, American Legion Post 65, Consumer Peer Reviewer, FY22***

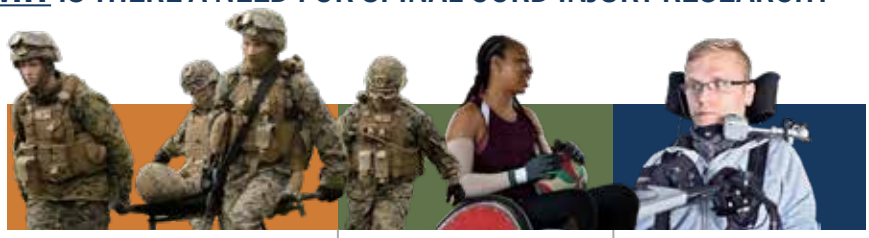
# SPINAL CORD INJURY RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in 2009, the Spinal Cord Injury Research Program (SCIRP) focuses on advancing research that addresses regeneration, rehabilitation, and long-term care across the life span of people living with a spinal cord injury.

| *FY22 Congressional Appropriations* |
|---|
| **$40M** |
| *FY22 Research Investment* |
| Clinical Trial Award ..... $16,410,335 |
| Investigator-Initiated Research Award ..... $7,846,474 |
| Translational Research Award .. $12,275,063 |
| Modification to ongoing awards ..... $4,985 |
| **Total:** $36,536,857 |
| *FY22 Withholds and Management Costs* |
| USAMRDC ..... $773,300 |
| SBIR/STTR ..... $1,335,000 |
| Mgt Costs (3.58%) ..... $1,354,843 |
| **Total:** $3,463,143 |

## WHY IS THERE A NEED FOR SPINAL CORD INJURY RESEARCH?



The rate of spinal cord injuries within the military was **8-10X** that of the civilian population at the height of the conflicts in the Middle East[1]

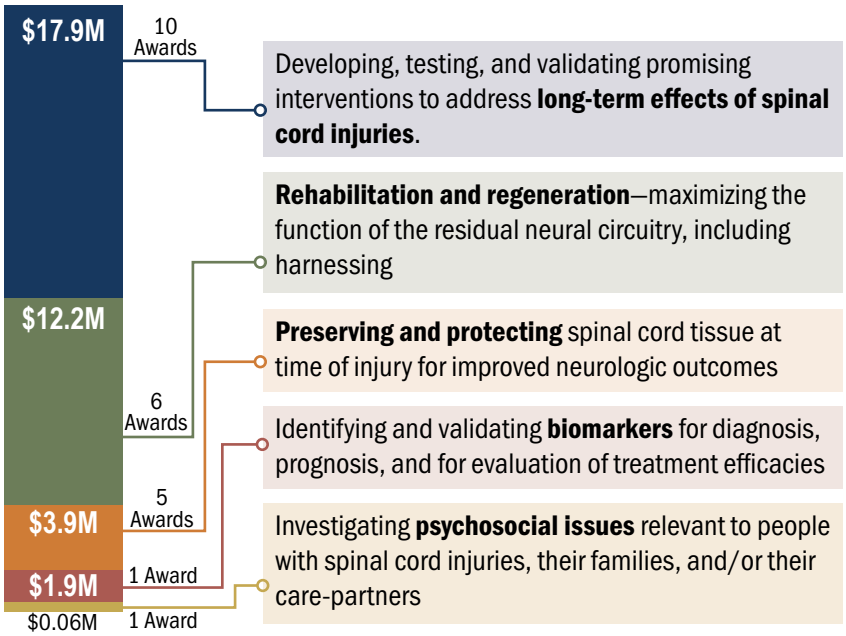
Roughly **20%** of all people in the U.S. with spinal cord injuries are Veterans[2]

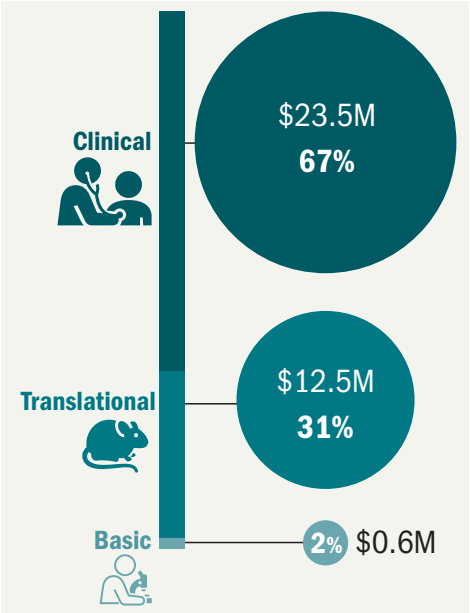
The VA is the largest single provider for spinal cord injury care in the U.S.[2]

- Spinal cord injuries are **complex** neurotraumatic wounds with long-term consequences affecting those living with the injury, their Families and care partners
- Nearly **300,000** individuals in the U.S. are living with a spinal cord injury[3]
- Around **18,000** new cases occur in the U.S. each year[3]
- On average, someone in the U.S. suffers an injury every **30 minutes**[3]

## HOW IS THE PROGRAM ADVANCING SPINAL CORD INJURY RESEARCH?

The SCIRP directed FY22 investments across five program priorities (left) and three stages of science (right).



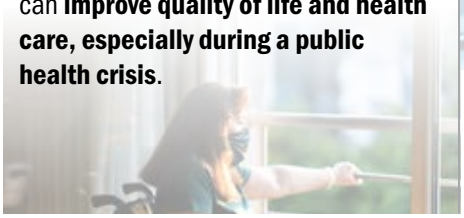
**PROGRAM MISSION:** *To fund research and encourage multidisciplinary collaborations for the development and translation of more effective strategies to improve the health and well-being of Service Members, Veterans, and other individuals with spinal cord injury*

## HOW IS THE PROGRAM MAKING AN IMPACT?

### *Loneliness and Its Relation to Health in People with Spinal Cord Injury*

*Susan Robinson-Whelen, Ph.D., Baylor College of Medicine*

Robinson-Whelen is examining the relationship of psychological and physical health to loneliness in a national longitudinal, 1-year survey of ~350 individuals with traumatic spinal cord injury. Based on the survey results, **the COVID-19 pandemic adversely affected quality of life and psychosocial well-being with reports of increased stress, depressed mood, anxiety, and loneliness**. This is especially concerning given that people with SCI are known to have higher levels of stress, depression, anxiety, and loneliness even without a pandemic. Decreased access to regular health care and increased health risks for in-person clinic visits during the pandemic may have further compounded the negative effects on mental health. Increased awareness of the unique needs of those living with spinal cord injuries can **improve quality of life and health care, especially during a public health crisis**.



### *Effects of Ekso-Assisted Gait Training on Bone Health and Quality of Life: A Randomized Clinical Trial*

*Leslie Morse, D.O., Craig Hospital*

As exoskeleton-assisted walking becomes more common for use in rehabilitation and in daily life, a more accurate understanding and monitoring of bone health is critical to avoid fractures. Dr. Morse's multi-site clinical trial suggests **computerized tomography imaging may outperform other types of imaging for predicting bone fracture risk in adults with spinal cord injuries.** Additionally, the researchers found that after 6 months of using exoskeletons to exercise via gait training, study participants showed signs of increased neural activity and experienced increases in bone mineral content indicating new bone formation. These outcomes informed **new clinical practice guidelines** and will serve as the basis for future clinical trials exploring robotic gait training to improve outcomes in patients with spinal cord injuries.

### *Epidural Stimulation and Resistance Training for Overground Locomotion After Spinal Cord Injury*

*Ashraf Gorgey, M.P.T., Ph.D., Virginia Commonwealth University*

In a recent pilot clinical trial, Gorgey tested an exoskeleton-assisted walking device paired with spinal cord epidural stimulation on individuals with spinal cord injury. **Two participants with chronic complete spinal cord injury demonstrated an increased ability to voluntarily control muscles below the injury site.** One participant achieved independent standing, independent stepping in parallel bars, and assisted walking. These early results indicate spinal cord epidural stimulation is a promising approach when combined with physical rehabilitation to increase independent movement and improve quality of life.

"My involvement helped me to realize that there are really people and programs existing that are actively awaiting real-life input regarding mental and physical disabilities so that advancements can be made to better the quality of life of individuals facing those issues."

***Retired U.S. Air Force Airman 1st Class Sean Ferry, Louis Stokes Cleveland VA Medical Center, FY16-19 and FY22 Consumer Peer Reviewer***

[1] U.S. Medicine. 2021. VA Meets Challenge: Pressure Injuries in Veterans with Spinal Cord Injuries. https://www.usmedicine.com/clinical-topics/wound-care/va-meets-challenge-pressure-injuries-in-veterans-with-spinal-cord-injuries/. | [2] VA Health Services Research & Development. 2013. Spotlight: Improving Care for Veterans with Spinal Cord Injuries and Disorders. https://www.hsrd.research.va.gov/news/feature/sci.cfm. | [3] National Spinal Cord Injury Statistical Center. 2023. Traumatic Spinal Cord Injury Facts and Figures at a Glance 2023. https://www.nscisc.uab.edu/.

# TICK-BORNE DISEASE RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in 2016, the Tick-Borne Disease Research Program (TBDRP) supports innovative and impactful research that addresses fundamental issues and gaps in tick-borne diseases.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$7M** | |
| *FY22 Research Investment* | |
| Idea Development Award | $2,494,008 |
| Therapeutic/Diagnostic Research Award | $3,694,274 |
| **Total:** | $6,188,282 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $135,320 |
| SBIR/STTR | $234,000 |
| Mgt Costs (6.67%) | $442,398 |
| **Total:** | $811,718 |

"I'm incredibly grateful for the innovative and cutting-edge research CDMRP enables. This critical research provides hope and ultimately solutions for DOD members and their families as they face medical challenges comparable to combat."

***U.S. Air Force Maj. Anders Karlsen, Center for Lyme Action, Consumer Peer Reviewer, FY21-FY23***

## WHY IS THERE A NEED FOR TICK-BORNE DISEASE RESEARCH?

In the U.S., **>50,000** cases of tick-borne diseases occur each year[1]

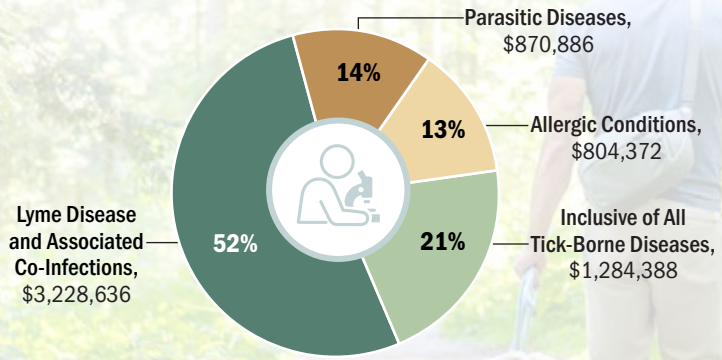
Over a 14-year period, **~6,000** Service Members and nearly **56,000** beneficiaries received a diagnosis of a reportable tick-borne disease,[2] and of these...

Lyme disease accounted for **~80%** of these diagnoses

- Reported cases of tick-borne diseases likely underrepresent the total number of infections, as the number of people treated for Lyme disease is **~476,000** annually based on insurance records in the U.S.[3]
- At least **20** known conditions can result from tick bites, including **13** illnesses caused by at least **18** tick-borne infectious pathogens[4]
- Tick populations are increasing and geographically expanding; as a result, new tick-borne diseases will emerge and disease incidence will rise[5]

## HOW IS THE PROGRAM ADVANCING TICK-BORNE DISEASE RESEARCH?

In FY22, the TBDRP directed investments into four disease categories.




[1] Centers for Disease Control and Prevention. 2021. https://www.cdc.gov/ticks/resources/Reported-Tickborne-Disease-Cases-by-County-of-Residence_2016-2019.xlsx. | [2] Data from the Armed Forces Health Surveillance Division for the years 2006-2020. | [3] Kugeler, KJ, Schwartz, AM, et al. 2021. Estimating the Frequency of Lyme Disease Diagnoses, United States, 2010-1018. *Emerging Infectious Diseases* DOI: 10.3201/eid2702.202731. | [4] Tick-Borne Disease Working Group. 2018. U.S. Department of Health and Human Services. https://www.hhs.gov/sites/default/files/tbdwg-report-to-congress-2018.pdf. | [5] Beard CB, Eisen L, and Eisen RJ. 2021. The Rise of Ticks and Tickborne Diseases in the United States - Introduction. *Journal of Medical Entomology* 58:1487-1489. https://doi.org/10.1093/jme/tjab064.

**PROGRAM MISSION:** *To understand the pathogenesis of Lyme disease and other tick-borne illnesses and conditions, and to deliver innovative solutions to prevent, diagnose, and treat their manifestations for the benefit of U.S. Service Members and the American public*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Vaccine**

***Development of a Live Attenuated Powassan Virus Vaccine***
*Margaret MacDonald, M.D., Ph.D., Rockefeller University*
Dr. MacDonald and her team worked to advance the **development of a vaccine for Powassan virus, which can infect the brain and cause neurological issues**. Recent results published in the journal *Vaccines*[6] demonstrated increased survival for mice administered the team's vaccine with **100% survival** observed for animals receiving a **prime-boost vaccination regimen** and **70% survival** for animals receiving a **two-dose vaccination regimen**. The prime-boost strategy included an initial vaccination to stimulate the immune system (prime) and a second vaccination containing a protein associated with Powassan virus infection to further stimulate the protective effects of the immune system. This work establishes a **novel vaccination strategy that lays the groundwork for further development of a potential Powassan virus prophylactic in humans**.

**Babesiosis Pathology**

***Analysis of the Peripheral Blood Transcriptome to Identify Clinical Correlates of Pathology in People Living with Babesiosis***
*Dana Mordue, Ph.D., New York Medical College*
Mordue and team enrolled people who presented with **babesiosis, a disease caused by parasites that infect red blood cells**, in a study to correlate host RNA signatures and disease symptom severity. Analysis of participant blood samples published in *Open Forum Infectious Diseases* showed a distinct difference in RNA profiles from uninfected participants and those with babesiosis. In people with babesiosis, blood profiles indicate **increased red blood cells** and transcriptional pathways associated with **damage to the heart, liver, and kidneys**. Additionally, surveys reported **decreased cognition and deteriorated quality of life** even after receiving treatment. These results provide **insight into babesiosis pathology** and suggest **further studies should focus on long-term impacts on quality of life.**

**Diagnostic Test**

***Development of a Highly Sensitive and Specific Acute Diagnostic Test for Tick-Borne Rickettsioses***
*Rong Fang, M.D., Ph.D., University of Texas Medical Branch, Galveston*
Currently, there is no timely diagnostic lab test for **tick-borne rickettsioses**, a group of diseases caused by various species of Rickettsia bacteria, resulting in fatal cases and significant morbidity due to delays in administering antibiotic. Dr. Fang made substantial progress in developing a **rapid and easy-to-perform test to detect a rickettsial diagnostic marker** at the early stage of rickettsioses using experimental animal models. The team is collaborating with scientists from the Centers for Disease Control and Prevention, Brazil, and other locations to validate the test using patient samples. This test will enable **timely and differential diagnosis of rickettsioses from a group of infections with similar symptoms, thereby reducing misdiagnoses and ensuring effective treatment**.

**Immune Response**

***A Longitudinal Systems-Level Analysis of the Human Immune Response During Lyme Disease***
*Naeha Subramanian, Ph.D., Institute for Systems Biology*
In people with Lyme disease, 10-20% will develop **post-treatment Lyme disease syndrome**, characterized by persistent symptoms for six or more months after antibiotic treatment, though the cause remains unclear. Subramanian characterized the **acute immune response to Lyme disease** and is exploring whether and how **immune dysregulation** may contribute to syndrome development. Using blood samples from patient cohorts tracked over time, the team analyzed distinct immune cell populations and assessed differential immune system activity in Lyme disease patients over time. This research will contribute to **improved host-based diagnostic biomarkers of Lyme disease to accurately diagnose infection earlier** and the development of new **treatments that are milder than broad spectrum antibiotics like doxycycline**, which can contribute to antibiotic resistance if overused or misused.

[6] Cheung AM, Yip EZ, et al. 2023. Characterization of Live-Attenuated Powassan Virus Vaccine Candidates Identifies an Efficacious Prime-Boost Strategy for Mitigating Powassan Virus Disease in a Murine Model. *Vaccines* (Basel) 8;11(3):612. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10058527/. | [7] Marcos LA, Lamba P, et al. 2022. Peripheral Blood RNA Dignatures Aassociated with Human Babesiosis, Quality of Life, and Neurological Symptoms. *Open Forum Infectious Diseases* Vol. 9, No. https://doi.org/10.1093/ofid/ofac492.563. Supplement: https://academic.oup.com/ofid/article/9/Supplement_2/ofac492.563/6902911.

# TOXIC EXPOSURES RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

Established in FY22, the Toxic Exposures Research Program (TERP) provides solutions toward the prevention, diagnosis, treatment, and mechanistic understanding of the adverse health outcomes associated with a broad range of militarily relevant toxic exposures impacting the health of our Service Members, Veterans, and the American public.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$30M** | |
| *FY22 Research Investment* | |
| Investigator-Initiated Research Award | $13,692,062 |
| Translational Research Award | $13,205,799 |
| Clinical Trial Award | $- |
| **Total:** | $26,897,861 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $511,558 |
| SBIR/STTR | $1,001,000 |
| Mgt Costs (5.58%) | $1,589,581 |
| **Total:** | $3,102,139 |

## WHY IS THERE A NEED FOR TOXIC EXPOSURE RESEARCH?

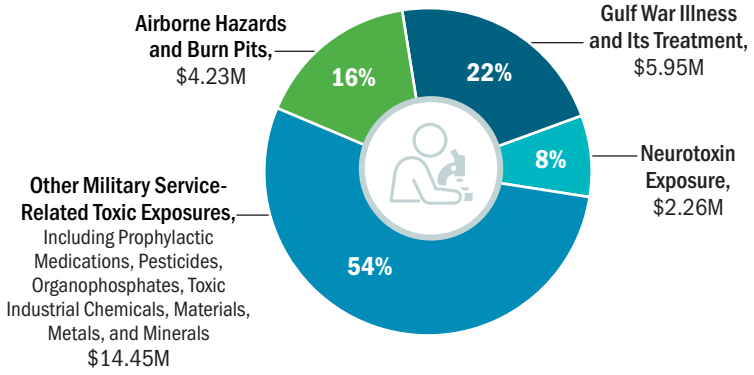
**Toxic exposures are known and unknown potentially harmful substances that Service Members may be exposed to during their military service**

**Outcomes of these exposures are not well defined and may impact the long-term health of Service Members**

- Since 1990, more than **3.7 million** U.S. Service Members deployed to combat environments with airborne hazards, such as burn pit emissions, oil-well fire smoke, vehicle exhaust, and sand[1]
- Service Members may also encounter toxic exposures in non-deployment settings

## HOW IS THE PROGRAM ADVANCING TOXIC EXPOSURE RESEARCH?

The TERP directed FY22 investments into four program priorities (top) aligned to the program's overarching goals (bottom).




**ELUCIDATE MECHANISMS OF HOW TOXIC EXPOSURES RESULT IN ADVERSE EFFECTS**

**DIAGNOSE THE EFFECTS OF TOXIC EXPOSURES**

**PREDICT AND PREVENT TOXIC EXPOSURES**

**DEVELOP THERAPEUTICS, TREATMENTS AND STRATEGIES**

[1] National Academies of Sciences, Engineering, and Medicine. 2020. Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. Washington, DC. *National Academies Press.* https://doi.org/10.17226/25837.

**PROGRAM MISSION:** *Support innovative and impactful research aimed at identifying and understanding the pathological mechanisms, outcomes and comorbidities associated with toxic exposures in order to facilitate the prevention, diagnosis and treatment of the invisible and visible diseases and symptoms that are associated with toxic effects impacting Service Members, Veterans and the American public*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Exposure Monitoring**

***Safeguarding Military Lives and Health via Superior Monitoring of Environmental and Personal Chemical Exposures***

*Evgueni Kadossov, Ph.D, XploSafe*

Kadossov and his team are developing the Xcel+ sampler, a **device that will sample a wide range of volatile chemicals** including, but not limited to, pesticides, fuels, and toxic industrial chemicals. This device is intended to be worn or placed in environments to monitor personal or general exposure to potentially harmful ambient chemical vapors. Xcel+ could aid in the **prevention of exposures** and help identify compounds Service Members are exposed to, thus facilitating timely diagnoses and intervention.

**Biomarker Identification**

***Identification of Metabolic Biomarkers of Gulf War Exposures and Gulf War Illness Using the DOD Serum Repository***

*Jennifer Rusiecki, Ph.D., Uniformed Services University of the Health Sciences*

Rusiecki intends to identify Gulf War-related toxic exposures by identifying chemical fingerprints left by small molecules called "metabolites" in pre- and post- deployment serum samples from Veterans living with Gulf War Illness and comparing to healthy controls. Serum samples will be obtained from the Department of Defense Serum Repository. Veterans will be identified using data collected by the Boston Biorepository and Integrative Network, or BBRAIN, patient. patient cohort, an effort supported by the CDMRP's former Gulf War Illness Research Program. The team will employ a technique called high-resolution metabolomics to **identify Gulf War-era environmental exposures and endogenous metabolites** that can be used as **biomarkers for diagnosis and as putative therapeutic targets.**

**Detoxification**

***A Novel and Practical Intervention for Detoxification of Per- and Polyfluoroalkyl Substances (PFAS) in Humans***

*Jennifer Schlezinger, Ph.D., Boston University*

PFAS are common chemicals used in water- and stain-repelling products, as well as in firefighting foams, which has led to long-lasting contamination of water supplies and poses considerable threat to military and civilian populations due to increased risk of cancer, liver damage, increased cholesterol in the blood and poor response to vaccines. Schlezinger aims to use **dietary fibers to prevent the absorption of and accelerate the elimination of ingested PFAS** in animal exposure models. If successful, the results from this study will serve as the foundation for follow-up studies in humans, which could ultimately identify a **cost-effective, straightforward to implement, noninvasive means to reduce the PFAS body burden** and potentially prevent associated adverse health effects.

"I am incredibly grateful to the Vietnam Veterans who welcomed me home from Desert Storm. They spoke out on our behalf when we came back with undiagnosed illnesses now understood as Gulf War Illness. I listened and learned so much from them in their struggle with the aftermath of Agent Orange and other tactical herbicide exposures. More recently, I have welcomed home a new generation of Veterans and listened to their concerns about toxic exposures, including airborne hazards, open burn pits, and other particulate matter exposures. It is my hope that the Toxic Exposures Research Program will expand the knowledge of and discover interventions for the many conditions and health concerns that Veterans experience and that the outcomes of the program will contribute to a better quality of life."

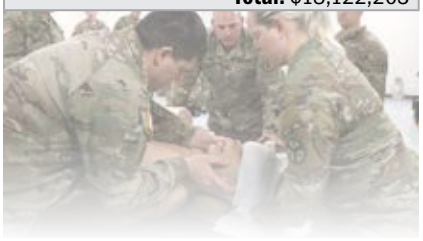
***Retired U.S. Air Force Tech. Sgt. Vera Roddy, Veterans of Foreign Wars, Programmatic Panel Member, FY22-FY23***

# TRAUMATIC BRAIN INJURY AND PSYCHOLOGICAL HEALTH RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

In FY07, the U.S. Congress appropriated funding for traumatic brain injury and psychological health, including post-traumatic stress disorder, in response to the TBIs sustained and psychological health issues experienced by our deployed forces in Iraq and Afghanistan. The Traumatic Brain Injury and Psychological Health Research Program (TBIPHRP) complements existing DOD research efforts in the prevention, detection, treatment, and rehabilitation of TBI and improved psychological health.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$175M** | |
| *FY22 Research Investment* | |
| Clinical Trial Award | $62,208,075 |
| Focused Program Award | $62,745,955 |
| Idea Development Award | $5,000 |
| Investigator-Initiated Research Award | $9,956,746 |
| Patient-Center Research Awards | $5,032,918 |
| Translational Research Award | $16,818,217 |
| Modification to ongoing awards | $110,886 |
| **Total:** | $156,877,797 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $3,379,024 |
| SBIR/STTR | $5,837,000 |
| Mgt Costs (5.37%) | $8,906,179 |
| **Total:** | $18,122,203 |

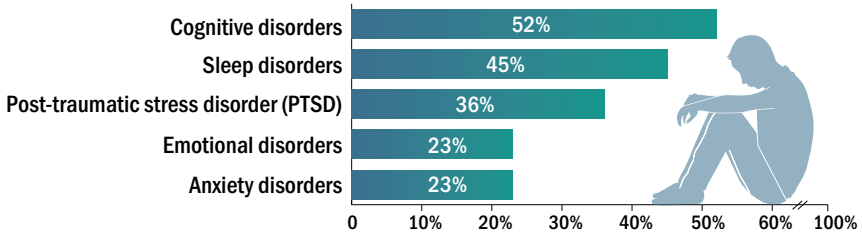


## WHY IS THERE A NEED FOR TRAUMATIC BRAIN INJURY AND PSYCHOLOGICAL HEALTH RESEARCH?

**More than 468,000 U.S. Service Members obtained a TBI diagnosis from 2000 to 2023**[1]

**In 2021, there were more than 2 million behavioral health-related medical encounters among active-duty members**[2]

Within 2 years of a TBI diagnosis, active-duty and reservists may be more likely to experience[3]:

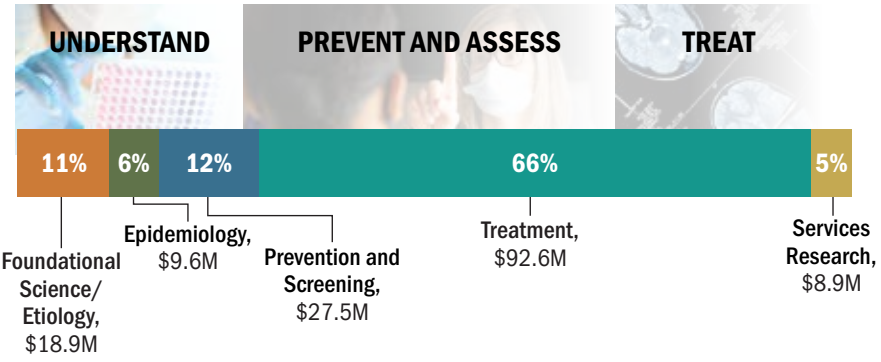





- **~3 million** Americans sustain a mild TBI each year[4]
- In 2020, civilians spent **over $280 billion** on mental health services in the U.S.[5]
- **~15.6%** of civilians diagnosed with TBI have PTSD[6]

## HOW IS THE PROGRAM ADVANCING TRAUMATIC BRAIN INJURY AND PSYCHOLOGICAL HEALTH RESEARCH?

In FY22, the TBIPHRP directed investments into five areas of the research and development continuum (bottom) addressing three program priorities (top).




[1] Military Health System and Defense Health Agency. 2023. DOD TBI Worldwide Numbers. | [2] https://www.health.mil/Reference-Center/Technical-Documents/2022/12/14/DOD-Health-of-the-Force-2021. | [3] Hai, T, Agimi, YII, & Stout, K. 2023. Prevalence of Comorbidities in Active and Reserve Service Members Pre and Post Traumatic Brain Injury, 2017-2019. *Military Medicine.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9825245/#sup1. | [4] Silverberg, N, et al. 2019. Management of Concussion and Mild Traumatic Brain Injury: A Synthesis of Practice Guidelines. *Archives of Physical Medicine and Rehabilitation* https://pubmed.ncbi.nlm.nih.gov/31654620/. | [5] The White House. 2022. Reducing the Economic Burden of Unmet Mental Health Needs. https://www.whitehouse.gov/cea/written-materials/2022/05/31/reducing-the-economic-burden-of-unmet-mental-health-needs/. | [6] Van Praag, DLG, Cnossen, MC, et al. 2019. Post-Traumatic Stress Disorder after Civilian Traumatic Brain Injury: A Systematic Review and Meta-Analysis of Prevalence Rates. *Journal of Neurotrauma*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6857464/.

**PROGRAM MISSION:** *Fund research to understand, prevent and treat psychological health conditions and/or traumatic brain injuries that accelerates solutions to improve the health and healthcare of Service Members, their Families, Veterans, and the American public*

## HOW IS THE PROGRAM MAKING AN IMPACT?

- Of the 62 funded awards enrolling human subjects, 79% involve active-duty and/or Veteran populations
- Nearly 30% of funded awards are involving people living with TBI throughout project planning and execution
- Five FY22 Patient Centered Research Awards address the barriers between promising research products and their implementation into clinical practice

***REACH-TBI: Addressing the Unique Needs of TBI Caregivers***
*Paul Perrin, Ph.D., University of Virginia*
Perrin and his team will adapt the Resources for Enhancing All Caregivers' Health, or REACH, intervention intervention to address the unique needs of the caregivers of Veterans and Service Members with TBI. To ensure REACH-TBI will address the unique needs of this population, the team will implement a community-based participatory research approach utilizing feedback from caregivers with lived experience, clinicians, VA clinical researchers, and VA administrative staff to design and refine the intervention. If successful, REACH-TBI will reduce the strain, depression, anxiety, and health care frustration that caregivers experience, as well as give clinicians a tool to **manage the needs of caregivers and Families over the entire course of the post-acute care continuum.**

***Photosensitivity as a Marker for Pain and PTSD Following TBI***
*Mary Heinricher, Ph.D., Oregon Health & Science University*
Heinricher will explore the link between heightened sensitivity to light, referred to as photosensitivity, and the "polytrauma clinical triad" of chronic pain, PTSD, and TBI. The project will evaluate photosensitivity as a possible quantitative marker of PTSD and chronic pain following TBI by measuring light sensitivity in Veterans and exploring its correlation with pain, poor sleep, and poor functional outcomes. This research has the potential to affect treatment strategies by offering **a new mechanism to assess treatment effectiveness and quality of life.** Additionally, data garnered from this proposal could also offer new insights into the effect of light on brain pathways in affected Veterans.

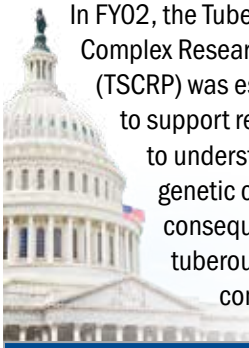
***Increasing Health Care Service Quality Through Improved, Evidence-Based Therapy Approaches***
*Shelley MacDermid Wadsworth, Ph.D., Purdue University*
This project seeks to improve the Star Behavioral Health Providers program, which connects military Service Members and their Families with licensed behavioral health professionals with training in military culture. To do this, MacDermid and her colleague David Riggs, Ph.D., at the Uniformed Services University of the Health Sciences will compare methods for delivering follow-on support to users. The project will focus on using cognitive behavioral therapy to treat insomnia and cognitive processing therapy to treat PTSD. If successful, this project will **identify strategies that could increase use of evidence based therapies** and **improve the quality of health care** by fostering connections between community clinicians and military personnel.

"As a combat Veteran that has been diagnosed with multiple mental health disabilities, I think this program is impacting the military and general public greatly with innovative and 'out-of-the-box' thinking that will provide support in so many ways to the Soldiers and civilians for years to come while incorporating their Families and communities."

***Retired U.S. Army 1st Sgt. Tomas Cruz, Ad Hoc Programmatic Reviewer FY22-FY23***

# TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

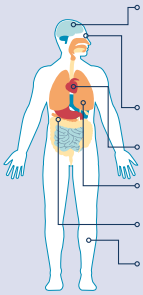


In FY02, the Tuberous Sclerosis Complex Research Program (TSCRP) was established to support research to understand the genetic causes and consequences of tuberous sclerosis complex.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$8M** | |
| *FY22 Research Investment* | |
| Clinical Translational Research Award | $2,756,455 |
| Exploration - Hypothesis Development Award | $1,216,611 |
| Idea Development Award | $3,135,168 |
| **Total:** | $7,108,234 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $136,525 |
| SBIR/STTR | $267,000 |
| Mgt Costs (6.43%) | $488,241 |
| **Total:** | $891,766 |

## WHY IS THERE A NEED FOR TUBEROUS SCLEROSIS COMPLEX RESEARCH?

Tuberous sclerosis complex is a rare genetic disorder caused by mutations in the TSC1 or TSC2 gene, causing tumor growth in multiple organs.



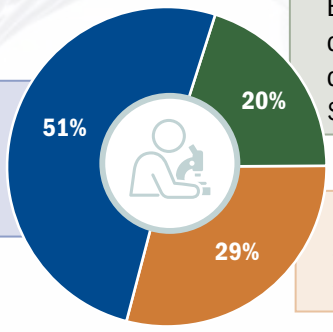
***Clinical manifestations include:***

- **Central Nervous System:** Autism, Intellectual Disabilities, Anxiety/Depression, Epilepsy, Cortical Tubers, etc.
- **Eyes:** Astrocytic Hamartomas
- **Heart:** Rhabdomyomas
- **Lungs:** Lymphangioleiomyomatosis
- **Kidneys:** Angiomyolipomas
- **Skin:** Skin Lesions

Currently **40,000-80,000** individuals in the United States and **1 to 2 million** individuals worldwide have TSC[1]

## HOW IS THE PROGRAM ADVANCING TUBEROUS SCLEROSIS COMPLEX RESEARCH?

The TSCRP directed FY22 investments into three program priorities.




Eradicating tumors and gaining a deeper understanding of signaling pathways and tumor microenvironment, $3,602,085

Expanding understanding of disease-associated neuropsychiatric disorders and reducing their impact, $1,426,801

Improving prevention, treatment, and neurodevelopmental outcomes of epilepsy, $2,082,578

"It has been a true privilege serving on the TSCRP panels as a Consumer Reviewer. I started my involvement with this program when my son, Bao, was 5 years old; he's now graduated high school and attending college. The impact this program has had over this period is nothing short of amazing! This is an extraordinarily well-managed and highly competitive grant process that delivers meaningful results for the tuberous sclerosis complex community. For me personally, participating in this program is the best thing I can do for my son."

***Ron Heffron, P.E., TSC Alliance, Programmatic Panel Member, FY13-FY23***

[1] National Organization for Rare Disorders. 2023 Tuberous Sclerosis Disease Overview: National Organization for Rare Disorders.

**PROGRAM MISSION:** *Support innovative and high-impact research that promotes discoveries in tuberous sclerosis complex, from mechanistic insights to clinical application across all age, by fostering new ideas and investigators for the benefit of Service Members, their beneficiaries, and the American public*

## HOW IS THE PROGRAM MAKING AN IMPACT?

**Therapeutic Target**


*Targeting mTOR/JUN/AXL Axis in Tumors*
*David Kwiatkowski, M.D., Ph.D., (left); Heng Du, M.D., (right)*
*Brigham and Women's Hospital*
Drs. Kwiatkowski and Du studied the role of JUN and AXL, a transcription factor and a protein kinase, in the development of tuberous sclerosis complex tumors. They found these proteins play an important role in relaying signals that cause tumors to grow. Additionally, the team discovered the use of the drug rapamycin to treat tumors while JUN and AXL signaling is active can cause tumors to regrow when rapamycin is stopped. R428, an inhibitor of AXL, **showed promising effects in inhibiting tumor growth** and caused less re-growth than rapamycin in some models. **This study laid the groundwork for additional research into the JUN/AXL pathway as a potential therapeutic target for tuberous sclerosis complex tumors**.

**Disease Manifestation**



*A New Mouse Model Sheds Light on the Origin of Epilepsy*
*David Sulzer, Ph.D. (left); James E. Goldman, M.D., Ph.D. (center); Guomei Tang, Ph.D. (right), Columbia University*
The research team sought to determine the cause of epileptic symptoms in patients living with tuberous sclerosis complex. While studying brains from a mouse model, the team found the disease is characterized by greatly enlarged cerebral cortical neurons, which can trigger epileptic seizures and are similar to cells seen in the brains of human patients. The research outcome **provides insights into the pathological and clinical features of the disease** and **informs future studies into its underlying molecular mechanisms.**

**Structural Biology**

*Structural Basis of Tuberous Sclerosis Complex Assembly and Dysregulation in Disease*
*Andrew Ellisdon, Ph.D., Monash University*
This project aimed to determine the basic structure of the TSC1-TSC2 protein complex responsible for regulating cell growth and proliferation and find the molecular basis of tuberous sclerosis complex's dysregulation in the disease. The team successfully determined the structure of the protein complex almost to the atomic level, which **will allow researchers to understand how structural changes caused by disease mutations affect signaling pathways and develop more effective targeted therapeutics.**

**Gene Therapy**

*Can Extracellular Vesicles Expand the Therapeutic Effect of Gene Replacement for TSC1 in Brain?*
*Xandra Breakefield, Ph.D., Massachusetts General Hospital*
This project aims to improve the effectiveness of a gene therapy technique in a tuberous sclerosis complex mouse model by utilizing microparticles in the body called extracellular vesicles. This therapy uses modified adeno-associated viruses, called viral vectors, to deliver healthy copies of the desired gene into cells. The extracellular vesicles **would allow for a more efficient gene replacement by allowing cells that received treatment to send healthy copies of the treatment protein to untreated cells within these vesicles**.

**Optimizing Care**

*Optimizing Therapeutic Control of Epilepsy Using a Novel Biosensor*
*Edward Chaum, M.D., Ph.D., Vanderbilt University Medical Center*
Dr. Chaum and his team aims to develop a first-in-class biosensor that accurately measures the level of certain drugs in blood and other bio-fluids. This device **works in real time and can be used in the clinic to assist physicians in assuring medication compliance and optimizing therapeutic doses to more effectively treat epilepsy symptoms while reducing the risk for drug toxicity**. This device may improve seizure control in patients living with refractory epilepsy from TSC and could be applied more broadly to the fields of neuropsychiatry, transplant medicine, and toxic overdoses seen in the emergency room setting.

# VISION RESEARCH PROGRAM

## WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

In order to implement therapeutic strategies to prevent or treat visual problems common to combat Soldiers, the Army needs to develop and validate compounds and strategies. Congress directs the Vision Research Program (VRP) to target the various causes, effects, and treatment of visual injury resulting from exposures to elements during combat operations and damage from explosive devices. This type of research will ultimately be used to ensure and sustain combat readiness.

| *FY22 Congressional Appropriations* | |
|---|---|
| **$20M** | |
| *FY22 Research Investment* | |
| Clinical Trial Award | $2,013,112 |
| Focused Translational Team Science Award | $5,553,561 |
| Investigator-Initiated Research Award | $7,493,070 |
| Translational Research Award | $1,435,449 |
| Translational Research Award - Pilot Clinical Trial | $1,646,466 |
| **Total:** | $18,141,658 |
| *FY22 Withholds and Management Costs* | |
| USAMRDC | $384,048 |
| SBIR/STTR | $667,000 |
| Mgt Costs (4.26%) | $807,295 |
| **Total:** | $1,858,342 |

"Military combat medics are charged with saving life, limb, and eyesight. Thanks to the emerging research from the VRP portfolio, their available tools are continually expanding, and increasingly impactful rehabilitative opportunities realized."

***Donald Overton, Blinded Veterans Association, Programmatic Panel Member, FY23***

## WHY IS THERE A NEED FOR VISION RESEARCH?

**Over a 10-year period,[1] at least**

**141,500**

**Service Members reported ocular system injuries**

**During the same period, other DOD beneficiaries reported**

**634,775**

**incidences of ocular system injuries**

**Of the reported incidences by Service Members and beneficiaries,**

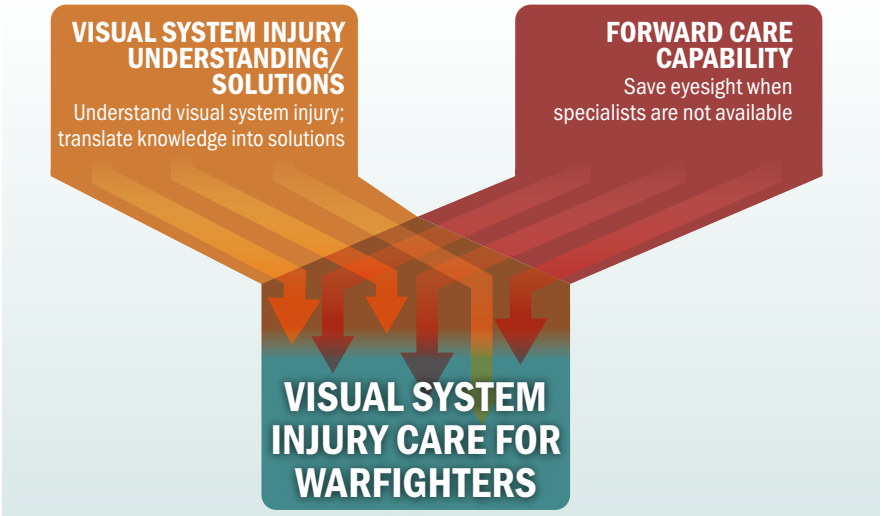
**~1,488**

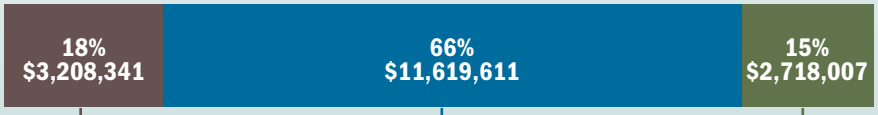
**were considered at high risk for blindness**

Over a 22-year period, **463,392** U.S. Service Members worldwide sustained TBIs, which can impair vision without direct injury to the ocular system[2]

## HOW IS THE PROGRAM ADVANCING VISION RESEARCH?

The VRP used the program's strategic plan (top) to direct FY22 investments into three program priorities (bottom).




**Understanding and treatment** of eye injury or visual dysfunction as related to military exposure

**Restoration of visual function** after military exposure-related vision loss or severe visual impairment

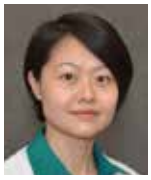
**Diagnosis, stabilization, and treatment** of eye injuries in austere environments and prolonged field care settings

**PROGRAM MISSION:** *To address clinical needs through innovative research targeting the mechanism, effects, and treatment of service-connected eye injuries and vision dysfunction*

## HOW IS THE PROGRAM MAKING AN IMPACT?

### VISION INJURY RESEARCH FORUM TELECONFERENCE

In April, the VRP hosted the inaugural meeting of the Vision Injury Research Forum, or VIRF, to provide a platform for investigators in the vision injury research field and military health medical professionals to engage in scientific exchange and foster communication and collaboration to improve the lives of those affected by vision loss. Investigators from around the world participated in the virtual meeting, including more than 40 DOD and VA medical providers. By bringing DOD and VA medical providers together with academic vision injury investigators and facilitating discussions of capabilities, gaps, state-of-science, and opportunities, the VIRF helps investigators gain better understandings of the needs of vision injury care for the military and Veterans to design the research to best address those needs.



### *Supersaturated Oxygen Emulsion as a Novel Topical Treatment for Ocular Chemical Injury*

*Jia Yin, M.D., Ph.D., M.P.H., Schepens Eye Research Institute*

In an effort to broaden the available options for treating chemically induced injuries to the eye, the research team developed a topically applied supersaturated oxygen emulsion, a topical spray treatment that contains suspended oxygen particles, and demonstrated the product to be compatible with human corneal cells. In a recently published article,[3] the team reported a single application **effectively mitigated acute chemical injury** in a mouse model, promoting corneal wound healing, reducing inflammation, and preserving ocular integrity and optical transparency. The novel treatment is a **promising therapeutic for expeditionary vision injury care in the military operational environment**.

### *Retinal Ganglion Cell Transplantation as a Treatment for TBI-Related Optic Nerve Injury*

*Donald Zack, M.D., Ph.D., Johns Hopkins University*

In order to innovate the understanding and treatment of military-related eye injuries, the VRP is investing in projects that leverage highly collaborative and multidisciplinary teams. This award, led by Dr. Zack, aims to develop cell replacement therapy for **optic nerve regeneration**. This award combines four projects to synergistically advance four critical elements needed for successful optic nerve regeneration: (1) improving differentiation and survival of stem cell-derived tissues, (2) improving retinal integration and synaptic function of transplanted human retinal ganglion cells, (3) optimizing the microenvironment to boost cell survival, and (4) translating these findings into two clinically relevant models of traumatic optic neuropathy. If successful, these complimentary efforts will establish a strong foundation to advance this **viable vision restorative therapy towards clinical implementation**.

### *Topical Application of Losartan: An Effective Treatment for Injury-Related Scarring*

*Steven Wilson, M.D., Cleveland Clinic Foundation*

Myofibroblasts, cells that aide in wound healing, cause corneal scarring when continually stimulated by the signaling protein TGF-β. Dr. Wilson assessed the effect of topical application of Losartan, an FDA-approved inhibitor of TGF-β, on corneal scarring in an animal model. **Results indicated Losartan prevents scarring and reduces corneal haze post-injury**. Based on foundational funding from the CDMRP, this work led to a provisional patent and provided scientific rationale for follow-on clinical evaluation of Losartan in patient populations for treating corneal injuries.

[1] Frick KD, Singman EL. 2019. 2019. Cost of Military Eye Injury and Vision Impairment Related to Traumatic Brain Injury: 2001–2017. *Military Medicine* 184(5-6):e338-e343. | [2] 2023. Data collected from 2000-2022 from Traumatic Brain Injury Center of Excellence https://www. health.mil/About-MHS/OASDHA/ Defense-Health-Agency/ Research-and-Development/ Traumatic-Brain-Injury-Center-of-Excellence/DoD-TBI-Worldwide-Numbers. | [3] Li S, Pang K, et al. 2022. Perfluorodecalin-Based Oxygenated Emulsion as a Topical Treatment for Chemical Burn to the Eye. *Nature Communications* 13:7371. https:// doi.org/10.1038/ s41467-022-35241-1.

# APPENDIX A: FY22-FY23 PROGRAM SUMMARY

*Table A-1. CDMRP Programs, Appropriations, and Applications Received and Awarded in FY22-FY23*

| Research Programs Managed by the CDMRP | FY22 | | | FY23 | |
|---|---|---|---|---|---|
| | Funds Received (in millions) | Applications Received | Applications Funded | Funds Received (in millions) | Applications Received to Date |
| Alcohol and Substance Use Disorders | $4 | 6 | - | $4 | - |
| Amyotrophic Lateral Sclerosis | $40 | 74 | 41 | $40 | 76 |
| Autism | $15 | 80 | 11 | $15 | 124 |
| Bone Marrow Failure | $7.5 | 24 | 8 | $7.5 | 45 |
| Breast Cancer | $150 | 1,193 | 79 | $150 | 1,102 |
| Breast Cancer Research Semipostal(1) | $0.5 | - | 2 | $0.5 | - |
| Chronic Pain Management | $15 | 82 | 16 | $15 | 90 |
| Combat Readiness Medical Research | $10 | 51 | 4 | $5 | 82 |
| Duchenne Muscular Dystrophy | $10 | 62 | 10 | $10 | 32 |
| Epilepsy | $12 | 47 | 11 | $12 | 69 |
| Hearing Restoration | $10 | 36 | 10 | $5 | 38 |
| Joint Warfighter Medical(2) | $40 | 61 | 4 | $25 | 47 |
| Kidney Cancer | $50 | 180 | 53 | $50 | 284 |
| Lung Cancer | $20 | 303 | 39 | $25 | 303 |
| Lupus | $10 | 40 | 13 | $10 | 55 |
| Melanoma | $40 | 163 | 40 | $40 | 218 |
| Military Burn | $10 | 50 | 4 | $10 | 47 |
| Multiple Sclerosis | $20 | 90 | 24 | $20 | 129 |
| Neurofibromatosis | $20 | 58 | 29 | $25 | 96 |
| Orthotics and Prosthetics Outcomes | $20 | 38 | 10 | $15 | 45 |
| Ovarian Cancer | $45 | 274 | 56 | $45 | 270 |
| Pancreatic Cancer | $15 | 88 | 22 | $15 | 123 |
| Parkinson's | $16 | 96 | 15 | $16 | 125 |
| Peer Reviewed Alzheimer's | $15 | 72 | 16 | $15 | 114 |
| Peer Reviewed Cancer | $130 | 490 | 99 | $130 | 549 |
| Peer Reviewed Medical | $370 | 1,288 | 163 | $370 | 1,500 |
| Peer Reviewed Orthopaedic | $30 | 93 | 21 | $30 | 114 |
| Prostate Cancer | $110 | 480 | 98 | $110 | 518 |
| Rare Cancers | $17.5 | 238 | 36 | $17.5 | 281 |
| Reconstructive Transplant | $12 | 70 | 11 | $12 | 73 |
| Spinal Cord Injury | $40 | 151 | 23 | $40 | 156 |
| Tick-Borne Disease | $7 | 30 | 6 | $7 | 38 |
| Toxic Exposures | $30 | 242 | 32 | $30 | 259 |
| Traumatic Brain Injury and Psychological Health | $175 | 310 | 66 | $175 | 244 |
| Tuberous Sclerosis | $8 | 43 | 11 | $8 | 60 |
| Vision | $20 | 67 | 11 | $20 | 57 |
| **Total** | **$1,545** | **6,670** | **1,094** | **$1,524** | **7,363** |

(1) Breast Cancer Semipostal funds applications received and reviewed by the BCRP.

(2) Joint Warfighter Medical Execution Management Breakdown: five awards funded with 6.3 dollars, six awards funded with 6.4 dollars and 3 mods managed by CDMRP.

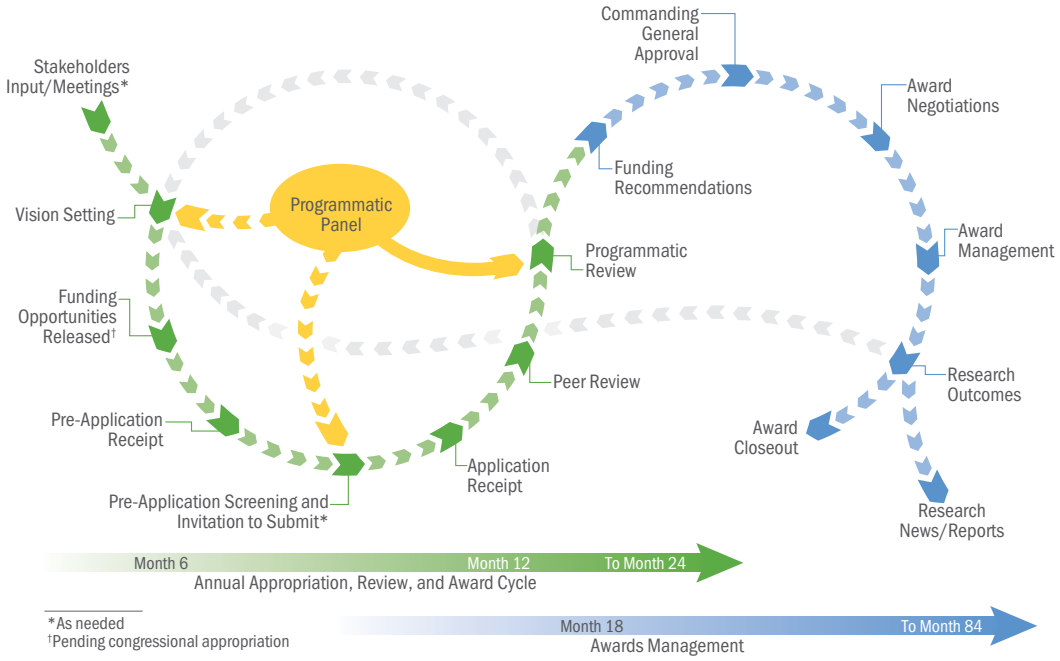
(3) FY23 Peer Reviewed Cancer Research Program: The agreement provide $130.0M for a peer-reviewed cancer research program to research cancers not addressed in the breast, prostate, ovarian, and lung cancer research programs currently executed by the Department of Defense. The funds provided in the Peer Reviewed Cancer Research Program are directed to be used to conduct research in the follow areas: bladder cancer, blood cancers, brain cancer, colorectal cancer, endometrial cancer, esophageal cancer, germ cell cancers, head and neck cancer, liver cancer, lymphoma, mesothelioma, metastatic cancers, myeloma, neuroblastoma, pediatric, adolescent, and young adult cancers, pediatric brain tumors, sarcoma, stomach cancer, thyroid cancer, and Von Hippel-Lindau syndrome malignancies (excluding cancers of the kidney and pancreas).

*Continued on next page*

(4) FY23 Peer Reviewed Medical Research Program: The Secretary of Defense. in conjunction with the Service Surgeons General, is directed to select medical research projects of clear scientific merit and direct relevance to military health. Research areas considered under this funding are restricted to: arthritis, celiac disease, dystonia, eating disorders, eczema, Ehlers-Danlos syndrome, neuroinflammatory response to emerging viral diseases, endometriosis, epidermolysis bullosa, familial hypercholesterolemia, fibrous dysplasia/McCuneAlbright syndrome, focal segmental glomerulosclerosis, food allergies, Fragile X, frontotemporal degeneration, Guillain-Barre syndrome, hemorrhage control, hepatitis B, hereditary ataxia, hydrocephalus, hypercholesterolemia, inflammatory bowel diseases, interstitial cystitis, Lymphatic disease, lymphedema, malaria, maternal mental health, mitochondrial disease, myalgic encephalomyelitis/chronic fatigue syndrome, myotonic dystrophy, nephrotic syndrome, neuroactive steroids, non-opioid therapy for pain management, orthopedics, pancreatitis, peripheral neuropathy, polycystic kidney disease, pressure ulcers, proteomics, pulmonary fibrosis, respiratory health, rheumatoid arthritis, scleroderma, sickle-cell disease, sleep disorders and restriction, suicide prevention, trauma, tuberculosis, vascular malformations, and Von Hippel-Lindau syndrome benign manifestations.

# APPENDIX B: STAGES OF THE CDMRP MANAGEMENT CYCLE

Under the leadership of a CDMRP Program Manager, each program follows the management cycle described in detail below.




*CDMRP Management Cycle*

- **Funding Process** – CDMRP funding is not included in the DOD's annual budget request to Congress. Funding for CDMRP is specified in the Defense Appropriations Act.
- **Stakeholders Input/Meetings** – Stakeholders survey the research landscape and identify important gaps and research opportunities.
- **Vision Setting** – Programmatic Panel members discuss the state of the science, stakeholder needs, and historical areas of investment by the program as well as other funders; develop a recommended investment strategy to fill critical research gaps and meet program goals.
- **Funding Opportunity Release** – Specific fiscal year funding opportunities are made publicly available and detail programmatic intent; type of studies being requested; eligibility; submission requirements; and application review criteria.
- **Application Submission and Receipt** – Application submission consists of a two-step process requiring BOTH pre-application submission (which includes a letter of intent or a pre-proposal, as specified in the announcement) as well as full application submission. Detailed information regarding submission requirements is provided in the funding opportunity announcement.
- **Two-Tier Review Process** – Full applications undergo two tiers of review.
  - Tier I involves a peer review where each application is individually reviewed based on specific review criteria in the funding announcement to assess scientific merit. Reviewers include scientific/technical subject matter experts and consumer representatives.
  - Tier II involves Programmatic Panel members reviewing applications comparatively while considering additional programmatic factors such as adherence to the award mechanism, programmatic goals, portfolio composition, impact, and military relevance.

  More information can be found here: https://cdmrp.health.mil/about/2tierRevProcess
- **Funding Approval** – The Commanding General of the USAMRDC is the approval authority for all CDMRP awards recommended for funding.
- **Award Management** – CDMRP monitors awards for technical progress and compliance with award terms and conditions throughout their entire period of performance.

# APPENDIX C: RESEARCH STAGE DESCRIPTIONS

**Basic/Discovery Research** – Fundamental research for generating new ideas, knowledge, hypotheses, models, or preliminary data to support applied and more advanced research.

**Applied Research** – Research utilizing basic research findings to develop material and knowledge products to prevent, diagnose, or treat diseases and conditions. Includes testing using animal models and animal validation, as well as clinical research studies designed without an intervention.

**Technology Development** – The generation, modification, assessment, and testing of technology, either physical or virtual, or instruments or tools for clinical application or research.

**Translational Research** – Research for transfer and evaluation of results from the laboratory to the clinic. Research at this stage includes Investigational New Drug-enabling studies; Good Laboratory Practice efficacy studies; and absorption, distribution, metabolism, excretion, and toxicology evaluation.

**Clinical Research includes the following:**

- **Clinical Trials** – Late-stage applied research, including testing and refinement of material and knowledge products in human subject populations. A clinical trial is defined as a prospective accrual of patients where an intervention, such as a device, drug, biologic, surgical procedure, rehabilitative modality, behavioral intervention or other, is tested on a human subject for a measurable outcome with respect to exploratory information, safety, effectiveness, and/or efficacy. This outcome represents a direct effect on the subject of the intervention or interaction.
- **Behavioral/Psychosocial Research** – Studies describing knowledge, attitudes, and behavior in defined populations and assessing the relationships between behavioral and social functioning with disease initiation, detection/diagnosis, progression, treatment, prognosis, and rehabilitation.
- **Quality of Life Research** – Studies designed to understand factors contributing to quality of life, interventions designed to enhance quality of life, and/or the quality of life consequences resulting from actions by subjects/patients, caregivers, and/or providers among individuals coping with or at risk of disease.
- **Epidemiology/Public Health Research** – Covers population and subject/patient-based observational studies of the distribution and incidence of disease as well as the behavioral and/or biological determinants of disease risk, initiation, detection/diagnosis, progression, prognosis, and rehabilitation.

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For more information, visit: https://cdmrp.health.mil/

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